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THE AMERICAN PHYSIOLOGICAL SOCIETY

Abstracts of papers received from the Secretary of the Society. Since there will be no meeting in 1944 these papers are to be regarded as "read by title". For possible corrections in any of these abstracts see the next issue.

Dehydration exhaustion. E. F. ADOLPH, A. H. BROWN (by invitation) and H. RAHN (by invitation). *Dept. of Physiology, School of Medicine and Dentistry, Univ. of Rochester, Rochester, N. Y.* Men acclimatized to the desert who walked without drinking water became exhausted when they had lost (by sweating) from 4 to 8 per cent of their body weights. On days of maximal air temperature 105°F. this state was reached in 4 to 7 hours. Over 40 instances have been observed, most of them in the field, a few of them in the laboratory hot room.

Signs and symptoms of oncoming exhaustion were: weariness, irritability, dizziness, dyspnea, sensation of muscular fatigue, flushing, abdominal ache, accelerated heart rate (whether resting or walking), rising rectal temperature, reflex restlessness, cyanosis, and a feeling of heat oppression. Measures which reduced circulatory strain (*e.g.*, lying down, moving the legs) in small part alleviated the symptoms of dehydration exhaustion. Thirst sensations in these rapid dehydrations varied among individuals and were usually no more than moderately unpleasant. Controls who drank water freely, avoided exhaustion; those who experienced it were largely relieved in 15 minutes of drinking ad libitum.

During desert dehydration the blood volume (measured by dye injection and hematocrit) was markedly diminished; the serum was concentrated (measured by refractive index) about 2½ times as much as the body as a whole. Chloride and nonprotein nitrogen became concentrated in the serum in nearly the same proportions. Hence water alone seemed to be lost from the circulation. To this disproportionately large decrement in blood volume is attributed in large part the signs of peripheral circulatory failure. [*Work done under contract, sponsored by CMR, between OSRD and the University of Rochester. Field studies were made possible by various units of the U. S. Army.*]

Voluntary dehydration. E. F. ADOLPH and ASER ROTHSTEIN (by invitation). *Dept. of Physiology School of Medicine and Dentistry, Univ. of Rochester, Rochester, N. Y.* Men in the desert or in the laboratory hot room do not drink voluntarily as much water between meals as they lose by sweating. What inhibits them from drinking? When men periodically force-drank enough water to keep up the body weight, no diuresis developed, showing that water could be retained to the usual extent. Evidently the urge to drink was diminished.

Rates of sweating up to 300 grams per hour were usually equalled by drinking, if cool water and leisure were available. At greater rates, especially with physical work, the deficit of body water increased disproportionately. But after a deficit of about 4 per cent of body weight had been contracted, drinking tended to keep pace with water loss. Similarly, when water was denied until the end of the period of work, rehydration was incomplete. Yet if water was then forced, no water diuresis resulted.

When salt was taken either in the water or separately, voluntary dehydration also prevailed. Flavored water or warm water exaggerated the deficit.

The serum became concentrated in about the same proportion to loss of body weight whether dehydration was voluntary or compulsory.

Evidently water intake was displaced from its usual relation to the body's water content by rapid sweating. Voluntary dehydration is not due to inability to retain water, but is an anomaly of thirst, the urge to drink water. [*Work done under contract, sponsored by CMR, between OSRD and the University of Rochester. Field studies were made possible by various units of the U. S. Army.*]

Spontaneous and induced epileptiform seizures in dogs. FREDERICK M. ALLEN and OTIS M. COPE. *Dept. of Physiology and Biochemistry, New York Medical College.* A spontaneous convulsive disorder, called epilepsy by veterinarians, is fully as prevalent among dogs as epilepsy is among human beings. There is a definite pattern of such seizures, which is identical with the form of convulsions in the water intoxication discovered by Rowntree. Spontaneous attacks on this pattern, not resulting from water ingestion, have been described (Allen: J. Urol., **49**: 520, 1943) in dogs after partial nephrectomy with or without temporary clampings of the remnants.

It has been found that while all dogs are subject to water intoxication, the susceptibility varies widely among apparently normal individuals. Occasional dogs develop convulsions with far less than the average water dosage. Among the several hundred dogs tested, all those subject to spontaneous "epilepsy" were also abnormally sensitive to water administration. The water sensitiveness of dogs in which spontaneous convulsions were never

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seen may perhaps mark them as latent "epileptics." The most prominent factors causing or exciting convulsions are infections (especially distemper) and nervous influences. The attacks are best controlled by sedatives and salt.

Rowntree discovered that the suppression of urine by pituitrin is most conducive to water intoxication. Studies at Morristown were the first to demonstrate the retardation of water excretion with partial nephrectomy. The present experiments confirm the previously (Allen, l.c.) described susceptibility of some partially nephrectomized dogs to convulsions. Also in one instance an electroencephalographic curve suggestive of epilepsy was obtained in a curarized animal with water intoxication.

Changes in the hypophysis after hypothalamic lesions. T. H. ALPHIN and F. L. DEY (both introduced by W. F. Windle). *Inst. of Neurology, Northwestern Univ. Medical School, Chicago.* Large electrolytic lesions placed bilaterally with the Horsley-Clarke machine in the guinea pig's hypothalamus just caudal to the optic chiasma led to genital hypertrophy, marked follicular development and an "always open" vaginal membrane. A discrete lesion placed in the median eminence led to marked genital atrophy and an "always closed" vaginal membrane which opened cyclically upon administration of ovarian hormones but closed and remained so when these were discontinued.

Hypothesis of "always open," "always closed," unoperated estrus, and unoperated diestrus guinea pigs were fixed in Champy-Kull fluid, stained by the Severinghaus technique and compared histologically. A marked increase in acidophil cells was encountered in the "always open" series. This appeared to be associated with a decrease in number of chromophobe cells. The additional acidophils resembled those encountered at estrus and at the end of pregnancy in unoperated animals. The "always closed" series of glands contained many large, rather granular basophilic cells with cytoplasmic inclusion; other types of cells, especially acidophils, exhibited degenerative changes.

It would seem that the large lesions in the hypothalamus produced an exaggerated picture of estrus (except mating behavior, which the lesions, per se, abolished) and that destruction of the median eminence led to a picture of diestrus with correspondingly exaggerated cytologic changes in the hypophysis in the former condition. [*Aided by a grant from the Committee for Research in Problems of Sex, National Research Council.*]

Inhibition of the endocrine function of the chick thyroid. E. B. ASTWOOD, A. BISSELL (by invitation) and A. M. HUGHES (by invitation). *Depts. of Pharmacology and Medicine, Harvard Medical School, Boston, Mass.* Representative antithyroid compounds which had previously been found active in the rat were tested on chicks beginning during the first week of life. The substances were admixed with the food in various proportions and the chicks were sacrificed at intervals thereafter. Aniline derivatives—p-aminobenzoic acid and sulfadiazine had no detectable effect upon the thyroid gland, agreeing with the observations of Mackenzie and Mackenzie (Endocrinol. **32:** 185, 1943) on sulfaguanidine. Thioureylenes produced a marked enlargement and hyperplasia of the thyroid gland and a decrease in its iodine content. Thiouracil was the most active of the compounds tested; by comparison the activity of diethyl thiourea was approximately one third, thiourea one fifth and thiobarbituric acid less than one one-hundredth that of thiouracil. One-tenth per cent thiouracil in the food induced maximal thyroid enlargement; this began within a few days and continued for at least 10 weeks when the glands from treated animals averaged 2.83 grams —45 times the weight of the controls; body growth was not impaired. Larger doses of thiouracil resulted in less thyroid enlargement. When given as a 0.5 per cent mixture in the food, growth and development were markedly retarded; wattles, combs and spurs failed to develop, muscles were weak, joints hypermobile, and finally the chicks became unable to stand; depot fat was increased. A fringe of wing feathers grew during the first few weeks but the down persisted and body feathers did not appear. This condition is interpreted as a state of cretinism in this species.

The effect of age on the chloride and water contents of chick tissues. J. S. BARLOW (by invitation), S. J. SLINGER (by invitation) and J. F. MANERY. *Dept. of Animal Nutrition, Ontario Agricultural College, Guelph, Ontario and the Dept. of Biochemistry, Univ. of Toronto, Toronto, Canada.* The changes occurring in the chloride and water contents of chick tissues during the periods of growth and maturity, i.e., from 3 to 427 days, were investigated intensively; some analyses were also obtained on birds up to 5 years of age. All chicks used were of the same White Leghorn strain, were hatched at the same time and reared under identical conditions. In most cases 10 birds were sacrificed at each age and their tissues and sera analyzed. The results are expressed on a fat-free basis when necessary.

Both chloride and water diminished in concentration in skin, muscle, tendon and serum during the interval studied, the most striking changes occurring during the first month after hatching which is the period of rapid growth. During growth the calculated extracellular water of muscle decreased from 53 to 20 per cent, and of skin from 70 to 50 per cent of the fat-free wet weight of the tissue. It remained constant during maturity but seemed

to diminish again as senility approached. The alterations in tendon extracellular water were less striking but a slight decrease also occurred in old age.

Positive injury potentials in human skin. T. CUNLIFFE BARNES. *Dept. of Physiology, Hahnemann Medical College, Philadelphia.* The fundamental work of Burr confirmed the observations of Melchoir and Rahm (Zentralbl. f. Chir. **45**: 598, 1918) that skin wounds are electropositive contrary to the classical concept of negative injury current. Melchoir's theory that the positivity arises from granulation is contradicted by positivity of fresh injuries. A needle was thrust through the skin of the finger-tip in five successive punctures. Measurements of the electropositivity of the finger-tip compared to an uninjured finger-tip were: 23.4, 32.6, 36, 36.8 and 42.3 mv. Each puncture exposed the positive inner surface of the skin (see Barnes and Coe, Journ. Cell. Comp. Physiol. **15**: 125, 1940). The positivity of the wound arises from the inner surface of the intact skin measured through the damaged area. This can be demonstrated by the effects of warming the skin (which produces positivity). The wounded finger was 40 mv. positive to the homologous uninjured finger. The potential rose to 43.8 when the injured finger was warmed to 44°C. but a much greater change, from 40 to 15 mv., occurred when the uninjured finger was warmed to 44°C.

In the frog, cutting off the foot made the stump 10–20 mv. positive to the intact opposite leg. In man stasis of the circulation by a sphygmomanometer cuff had little immediate effect on the wound potential.

The positive injury potential disappeared when the wound healed. Two per cent allantoin, 40 per cent urea or 10 per cent sulfanilamide did not affect rate of healing. In some cases the potential was higher with allantoin and urea owing to dissolving of scab.

The effect of left-handedness, temperature, pressure and chemical agents on human skin potential. T. CUNLIFFE BARNES. *Dept. of Physiology, Hahnemann Medical College, Philadelphia.* The skin of the right hand in the majority of right-handed persons was electro-positive to that of the left (measured from the finger-tips), but in twenty left-handed persons ten were positive on the right, seven were positive on the left and three were isoelectric (average of finger to finger potentials). An index finger partially immobilized by injury to tendon twenty years previously was 10 mv. negative to all others. Warming the skin made the potential more positive, augmented when the circulation was arrested by a cuff (absence of thermoregulation by blood). At room temperature blocking the circulation usually produced negativity (the skin temperature fell to 28°C), but there is little evidence that the potentials measured are produced by ionized oxygen in the blood (Leiri, Skand. Arch. Physiol. **71**: 166, 1935) or by hydrogen ions in the blood (Snodgrass, Am. Journ. Physiol. **140**: 394, 1943).

Muscular contraction (with or without circulation) made the finger potential positive (5 to 15 mv.) due to pressure of the finger on the cup of saline serving as electrode. Clamping the relaxed finger gave the same effect. Pressure makes better contact with the positive potential of the inner surface of the skin (Barnes, Fed. Proc. **1**: 6, 1942).

Sanborn electrocardiograph paste made the skin 3–8 mv. negative confirming Beutner's studies on concentrated NaCl solutions. Mustard plaster produced 5 mv. positivity and raised the skin temperature 2°C. Musterole gave 5 mv. negativity. Chloroform made the skin negative by cooling; 10 per cent aluminum chloride produced 3–18 mv. negativity in spite of its antihidrotic action.

The effect of gastric and intestinal instillation of bile on gastric secretion. WM. D. BEAMER (by invitation), M. H. F. FRIEDMAN, J. EARL THOMAS and M. E. REHFUSS (by invitation). *Dept. of Physiology, Jefferson Medical College, Philadelphia.* Meyer, Ivy and McEnery (Arch. Int. Med. **34**: 129, 1924) found that bile stimulated gastric secretion when introduced into either the stomach or intestine of Pavlov-pouch dogs. They concluded that the action in both cases came from its effect in the intestine. Kaulbersz and Winfield (Federation Proc. **1**: 45, 1942) reported that bile placed in the stomach of Pavlov-pouch dogs increased the gastric secretion in response to histamine but that it inhibited gastric secretion when the bile progressed into the intestine.

Dogs provided with gastric and duodenal fistulas were used; one of the dogs also had a Pavlov pouch. Experiments were carried out only when the stomach showed absence of secretory activity. Fresh dog bile or 5 per cent ox bile was instilled into either the stomach or intestine. Adequate drainage of the duodenal cap prevented exchange between the stomach and intestine.

Bile introduced into the stomach in volumes of 50 to 300 cc. resulted in a secretion of gastric juice after a latent period of about 30 to 45 minutes. When introduced directly into the intestine, bile did not have any secretory effect except in those instances where it was permitted to regurgitate into the stomach. When bile was introduced into the intestine together with proteose solution, the secretory response was greater than when the proteose solution alone was instilled.

Effects of asphyxiation at birth on learning ability. R. F. BECKER and W. F. WINDLE. *Dept. of Anatomy and Inst. of Neurology, Northwestern Univ. Medical School, Chicago.* Controlled histopathologic studies have been made on brains of

guinea pigs which were asphyxiated at birth, resuscitated and subjected to a learning test at 4 to 6 weeks. The test was a simple alternation problem with food and cover as motivating factors. The animals had to learn that the exit was always behind a blind alley.

At present the brains of 36 experimental animals and their litter-mate controls have been studied. Definite pathologic changes were observed in 23. On the maze tests, 19 of these 23 were inferior to their litter-mate controls. Some could not learn the simple problem at all. Others quickly forgot the solution. None was superior to its control. All controls learned the problem readily and remembered it well. Failure in learning tests was often correlated with extensive nerve-cell loss in sensory areas such as thalamic nuclei and geniculate bodies. In others the damage was predominately cortical. [*Aided by grants from The Women's Faculty Club and Medical Abbott Fund of Northwestern University Medical School.*]

Relative Renotropic and Testoid Activity of Various Steroids. E. BELAND (by invitation), G. MASSON (by invitation) and H. SELYE. *Dept. of Anatomy, McGill Univ., Montreal, Canada.* In a series of steroids we estimated the renotropic potency by the increase in kidney weight and the testoid activity by the increase in seminal vesicle weight, both these being expressed as percentage increase over normal. Each steroid was tested on a group of 8 to 10 castrate male Swiss Albino mice weighing 13 g. The steroids were administered subcutaneously in the form of 3 pellets each weighing 10 mg. and prepared under 200 lbs. pressure. The organs and the remnants of the pellets were weighed on the 30th day of the experiment. The results summarized in the preceding table indicate that methylandrostane-3(α), 17(α)-diol and, to a lesser extent, the corresponding non-ethylated compound have the most favorable $\frac{\text{renotropic}}{\text{testoid}}$ ratio.

Compound	Amount absorbed in mgm.	% increase in kidney weight	% increase in kidney weight per mgm. absorbed	% increase in seminal vesicles weight	% increase in seminal vesicles weight per mgm. absorbed
α-estradiol	4.1	−27.0	−6.6	210	50.0
Androstane-3(β), 17(α)-diol	6.1	5.3	0.87	37	16.5
Cis-testosterone ac.	14.6	−17.2	−1.2	28	2.0
Δ^5-androstene-3(β), 17(β)-diol	6.2	−10.5	−1.7	3	0.5
Δ^5-androstene-3(β), 17(α)-diol dipr.	2.3	−5.0	−2.2	80	35.0
Trans-dehydro-iso-androsterone	20.5	−4.6	−0.2	10	0.5
Progesterone	12.7	9.5	0.7	0	0
Δ^5-pregnene-3(β)-ol-20-one	1.9	1.0	0.5	0	0
Acetoxypregnenolone	6.9	−2.0	−0.29	0	0
Ethynyl-testosterone	0.9	2.3	2.5	10	10
Ethynyl-Δ^5-androstene-3(β), 17(α)-diol	2.5	−4.0	−1.6	0	0
Etiocholane-3(β)-ol-17-one	19.3	10.0	0.5	0	0
Δ^5-androstene-3(β), 17(α)-diol	4.4	15.0	3.4	0	0
Cis-testosterone	9.9	15.5	1.7	0	0
Methyl-Δ^5-androstene-3(β), 17(α)-diol	3.6	15.8	4.4	52	14.7
Androstane-3, 17-dione	23.6	22.0	0.93	740	310.0
Desoxycorticosterone ac.*	19.7	27.0	1.4	0	0
Δ^4-androstene-3, 17-dione	19.4	50.0	2.5	4000	206.0
Testosterone pr.	3.1	50.5	16.1	3000	970.0
Testosterone	14.2	58.3	4.1	5700	400.0
Methyl-androstane-3(α), 17(α) diol	6.6	63.0	9.5	1920	290.0
Androstane-3(α), 17(α)-diol	3.1	67.3	21.4	2200	710.0
Methyl-testosterone	17.6	74.0	4.2	5800	330.0

* In this case renal enlargement due to nephrosclerosis.

The effect of succinate and malonate on the duration of baributrate narcosis. KARL H. BEYER and ALBERT R. LATVEN (by invitation). *From the Dept. of Pharmacology, the Medical-Research Division, Sharp and Dohme, Inc., Glenolden, Pa.*

Since certain barbiturates inhibit the oxidation by brain tissue of lactate, pyruvate and glucose, but not of succinate, it was suggested by Soskin and Taubenhous (J. Pharmacol., **78:** 49, (1943)) that sodium succinate might be used as an antidote for barbiturate poisoning and to control the duration of anesthesia. This view was supported by their experimental data. We reasoned that if succinate decreased the duration of barbiturate anesthesia, malonate which competes with succinate for the same enzyme system, might prolong anesthesia.

In neither mice nor rats did sodium malonate (250–500 mgm./kgm. intramuscularly) prolong the duration of pentobarbital anesthesia significantly.

Sodium succinate produced a considerable shortening of pentobarbital narcosis only when administered in very large amounts. In two sets of 19 mice each in the control and in the succinate injected groups, an injection of 150 mgm./kgm. of sodium succinate intramuscularly immediately following the loss of the righting reflex failed to shorten the duration of anesthesia produced by sodium pentobarbital (80 mgm./kgm. intraperitoneally). When 1000 mgm./kgm. of sodium succinate was administered the significant difference between these animals and those given barbiturate alone was 5.25 (2.0 or more indicates a definite difference). In 'cross-over' experiments in rats given 30 mgm./kgm. of sodium pentobarbital intraperitoneally 250 mgm./kgm. of sodium succinate administered intramuscularly decreased the duration of narcosis in both groups. In a similar 'triple-cross-over' experiment involving injections of distilled water, sodium succinate (500 mgm./kgm.) and sodium malonate (500 mgm./kgm.) at weekly intervals the succinate shortened slightly the duration of narcosis (significant difference = 2.4), whereas malonate had no effect.

Changes in the iodine content and weight of the thyroid gland produced by thiouracil. A. BISSELL (by invitation) and E. B. ASTWOOD. *Depts. of Pharmacology and Medicine, Harvard Medical School, Boston, Mass.* Thiouracil administered to rats as a 0.1 per cent solution in the drinking water caused a rapid loss of iodine from the thyroid gland beginning within 24 hours and continuing regularly for 5 days when it reached a stabile concentration one-thirtieth that of normal. In 3 days the weight had increased 50 per cent and in 10 days 300 per cent; thereafter enlargement was slow. Omission of the drug after 8 days caused a significant reaccumulation of iodine in the first 24 hours, and within 7 days the weight and iodine concentration were near normal. Iodide added to the diet had no effect on the loss or reaccumulation of iodine. Dosage-response curves were constructed by the administration of thiouracil in concentrations of from 0.0001 per cent to 0.1 per cent in the drinking water for 10 days. A concentration of 0.0003 per cent produced a distinct decrease in iodine while 0.003 per cent to 0.01 per cent was required to induce a significant thyroid enlargement. The resulting curves have been used to determine the relative anti-thyroid activity of new compounds. In animals pretreated with thiouracil hypophysectomy or thyroxin treatment reduced thyroid size and induced the reaccumulation of colloid without altering the low iodine concentration. Thyrotropin injections in normal animals induced a more rapid enlargement of the thyroid but the iodine loss was at a slower rate than with thiouracil. Sulfadiazine was qualitatively similar to thiouracil. These findings indicate that thiouracil inhibits the production of thyroid hormone and prevents the accumulation of iodine in the gland.

The effect of adrenal cortical extract on blood non-protein nitrogen in shock produced by venous occlusion. J. E. BOURQUE (by invitation), S. JOSEPH (by invitation), C. P. KOZLOW (by invitation), JEAN HOUSTON (by invitation) and H. O. HATERIUS. *Dept. of Physiology, Wayne Univ., Detroit, Mich.* Observations were made upon the effect of adrenal cortical extracts on the blood NPN of dogs following occlusion of the venous drainage of one leg (Bourque, Haterius and Glassco 1943). ACE was given in doses of 1.5 cc./kgm. intramuscularly at 20 and at 2 hours preoperatively and similarly at 1 and at 5 to 8 hours following occlusion.

At the outset, blood pressure fell and NPN rose in the ACE-treated animals with slopes similar to those seen in untreated controls. Beginning at the 4th or 5th hour postoperatively, however, ACE retarded the fall in arterial blood pressure and the rise in NPN which characteristically follow the occlusion procedure. Thus, except for a time lag, the relation between blood pressure and blood NPN was essentially the same in both untreated and treated animals. The data tend to conform to the variable results reported on the efficacy of ACE in shock of non-adrenal origin, i.e. it was only in the occasional animal that blood pressure and NPN differed materially from the values found in untreated controls. The averages of the two groups did not differ significantly, although there was a significant difference in survival time.

Kidney function was affected almost equally in both sets of animals, the onset of oliguria signaling the rise in blood NPN. [*Aided by a grant from Parke, Davis & Company.*]

Demerol and cholinesterase. CLYDE O. BRINDLEY (introduced by G. S. Eadie). *Dept. of Physiology and Pharmacology, Duke Univ. School of Medicine, Durham, N. C.* Since both morphine and atropine inhibit the hydrolysis of acetylcholine by cholinesterase, it seemed probable that demerol, which combines important pharmacological properties of each, would also affect the reaction. This has been found to be the case. The enzyme solution was prepared by the method of Mendel and Rudney (Biochem. J. **37:** 59, 1943); details of experiments and calculations were given by Eadie (J.B.C. **146:** 85, 1942) except that 0.001 N instead of 0.01 N NaOH was used, and velocities were reckoned in terms of this. A typical experiment showed the initial velocity of hydrolysis of 0.00064 M acetylcholine to be 1.58 in absence of demerol: 0.65 in a solution containing 20 mgm. per cent, 0.44 mg. per cent and 0.31 in 80 mgm. per cent of demerol hydrochloride. While inhibition is probably competitive, data so far available are insufficient to decide this.

Water losses of men on life rafts. ALLAN H. BROWN and ROBERT E. GOSSELIN (introduced by E. F. Adolph). *Dept. of Physiology, School of Medicine and Dentistry, The Univ. of Rochester, Rochester, N. Y.* In warm seas, survival of castaways is often limited by bodily dehydration. Means of decreasing the loss of body water contribute to prolonged survival of men adrift. Use of shade and wetting of clothes with sea water have been suggested as methods of reducing evaporative loss of body water.

Rates of evaporative water loss were measured in 159 man-experiments on soldiers in rubber rafts near Florida. Air and surface-water temperatures, relative humidity, wind velocity, and degree of cloudiness were recorded. Meteorological conditions were relatively uniform; nearly all experiments were on clear days with sea breeze; the average air temperature was 85°F. Men were intermittently exposed to simulated emergency conditions and measurements were made at all times of day and night.

Rates of evaporative loss varied with time of

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day; they averaged 247 ± 7 gm./hr./man by day and 32 ± 3 gm./hr./man at night. These rates were not significantly reduced during prolonged exposure, while urinary water loss and rate of urinary solid excretion diminished in the first 30 hours of continuous dehydration without food.

Evaporative water losses were reduced by about 40 per cent when men were shaded with a tarpaulin. The practice of wetting the clothes diminished rates of evaporative loss in the sun by 74 per cent. Shaded men also benefited by wetting their garments, since daytime losses were then 83 per cent below those of dry, unshaded individuals. Since shade and wetting together can reduce to one-sixth the daytime rates of evaporative water loss, they may more than double the time of survival. [*Work done under contract, sponsored by CMR, between OSRD and The University of Rochester. Field studies were made possible by various units of the U. S. Army.*]

Changes in flicker fusion frequency (F.F.F.) under experimental stress. JOSEF BROZEK (by invitation) and ANCEL KEYS. *Laby. of Physiological Hygiene, Univ. of Minnesota, Minneapolis.* Validation of the F.F.F. as a test of "general fatigue" consists in relating the changes in fusion level to an imposed strain which can be expressed in such objective terms as degree of environmental temperature, amount of physical work and caloric debt. Under normal (standard) conditions the F.F.F. measurements were found satisfactorily repeatable and not significantly changed with practice. When 8 young men were subjected 10 times to 4 hours of hard work on the treadmill, interrupted by 3 rest pauses of 45–60 min., the F.F.F. at the end of the 4th hour of marching was *higher* than in the mornings, with the general average difference being +1.8 flickers per second. When 6 men were studied in experiments involving 3 days of work on the treadmill (3.25 m.p.h., 7.5 per cent incline) at a temperature of 120°F., humidity about 25 per cent relative saturation, the average A.M. scores on successive days were 49.3, 49.3, and 47.6 while the P.M. scores were 49.6, 48.8, and 48.0. When twelve men were kept for 3 days on a daily caloric intake of about 1,100 calories while the output was about 4,500 calories, the values obtained on successive mornings were 49.2, 48.4, and 48.2, and in the afternoons 48.5 and 47.6. Four men subjected to a similar work regime combined with total starvation had average scores of 56.2, 53.0 and 53.5 on successive mornings, and 56.8 and 53.8 in the afternoons. The F.F.F. decreases under prolonged stress but the changes are small and frequently not statistically significant.

Effect of anterior pituitary growth promoting extracts on blood amino acid N and blood uric acid in the pigeon. A. CANTAROW, K. E. PASCHKIS[1] and A. E. RAKOFF (by invitation). *Jefferson Medical College and Hospital, Philadelphia, Pa.* Anterior pituitary growth preparations have been shown to cause a decrease in blood urea and amino acid in dogs, rats and guinea pigs. This is generally attributed to an action of APE in stimulating anabolism or/and retarding catabolism of proteins. Blood amino N was determined in 19 pigeons and blood uric acid in 21 pigeons before and 6 hours after injection of APE (Antuitrin G). An increase in amino N occurred in 13 instances (average increase 2.8 mg. ±0.8) and in uric acid in 15 instances (average increase 6.5 mg. ± 2.4). Controls showed no significant variation during the experimental period.

Uric acid is, in part at least, an end product of protein catabolism in birds, analagous in this respect to urea in mammals. These findings raise the question as to whether APE may not enhance protein catabolism in the pigeon rather than protein anabolism, as has been suggested in mammals. These data are of interest because of the fact that doubts regarding the specific action of anterior pituitary growth hormone have been based in part on observations made on birds.

Survival time of rabbits after tourniquet occlusion of hind legs. ATTILIO CANZANELLI, RUTH GUILD (by invitation) and DAVID RAPPORT. *Physiology Dept., Tufts College Medical School, Boston.* Tourniquets were applied, shutting off both arterial and venous flow, to the hind legs of rabbits under light urethane anesthesia, augmented when needed by small doses of intravenous nembutal. The survival times following release of the tourniquets were as follows: after 2 hour occlusion at room temperature, the survival time in 14 experiments was 3.8 ± 0.6 hours; after 5 hour occlusion at room temperature in 19 experiments it was 1.7 ± 0.4 hours. When the legs were kept at 37°C. during 5 hour occlusion the survival time in 15 experiments was 1.2 ± 0.2 hours. When they were packed in ice during occlusion for the same time, it was 4.3 ± 0.7 hours in 14 experiments, while in 5 more, to which statistical methods seemed inapplicable, the survival time was greater than 24 hours. Preliminary observations indicate that the survival time is not affected by dehydration or fasting. In view of the predictability of the survival times, tourniquet occlusion in the rabbit appears to offer a promising technique for the study of shock.

The effect of temperature on the luminescent and non-luminescent reactions of luciferin. AURIN M. CHASE and PHILIP B. LORENZ (by invitation). *Physiological Laby., Princeton Univ., Princeton, N. J.* The bioluminescent reaction of purified

[1] J. Ewing Mears Fellow in Medicine and Physiology.

Cypridina luciferin and luciferase has been studied *in vitro* at five temperatures, from 8° to 36°C. An equation is developed representing the luminescent reaction of luciferin and luciferase and the non-luminescent oxidation of luciferin as first order reactions occurring simultaneously. The equation has the form:

$$x = \frac{k_1 a}{k_1 + k_2} [1 - e^{-(k_1+k_2)t}] \qquad (I)$$

x is total light emitted during the reaction up to any time t, and a is the total light that would have been emitted had all of the luciferin initially present reacted with luciferase in the luminescent reaction and had none been oxidized without luminescence. k_1 and k_2 are the velocity constants of the luminescent reaction and of the non-luminescent oxidation of luciferin, respectively.

The relationship,

$$x = \frac{k_1}{k_2} y, \qquad (II)$$

is also derived, for $t = \infty$, where x has the same meaning as in I, and y represents that fraction of the luciferin initially present which was oxidized without luminescence during the course of the experiment.

The values of k_1 and k_2 can be calculated for any temperature by simultaneous use of equations I and II, and the experimental measurements are well fitted by theoretical curves calculated using these values of k_1 and k_2 in equation I.

k_2 increases with temperature in fair agreement with the Arrhenius equation, while k_1 increases with temperature to about 25°C. and then decreases sharply with further increase of temperature, thus exhibiting an optimum similar to that for luminescence in certain bacteria.

A comparative study of clot firmness and clot retraction contacting foreign surfaces. ALFRED LEWIN COPLEY. *Division of Research Surgery, Dept. of Surgery and Gynecology, Univ. of Virginia School of medicine, Charlottesville.* Glass tubes of uniform length and internal diameter were employed without lining or were lined with paraffin oil, paraffin, or a synthetic plastic "Lusteroid." After the lower end had been stoppered, an equal volume of blood was placed in each tube and allowed to clot. The tubes were stoppered, not agitated, and incubated for one hour at 37°C. Then both stoppers were removed, and the degree of clot retraction noted. In case the clot adhered to the foreign surface, it was loosened with a fine long steel probe; care was taken not to cut the clot. Clot firmness was tested in triplicate with viscometer tubes according to the Lalich-Copley method (Proc. Soc. Exp. Biol. Med. **51**: 232, 1942). Blood was obtained from the jugular vein of 33 dogs; the first 10 cc. of blood was discarded.

No clot retraction occurred in Lusteroid lined tubes. In tubes lined with paraffin or paraffin oil, there was either no, partial, or strong syneresis. In glass tubes, clot retraction was observed, except when the blood clots were first incubated at 0°C. for 3 hours, and afterwards at 37°C. for one hour. Then, frequently, no, or only slight syneresis occurred, although marked syneresis was observed in paraffin lined tubes. Non-retracted blood clots often showed even higher clot firmness than retracted clots. The general contention that there is a relationship between the firmness and retraction of a blood clot could not be corroborated. These rheological phenomena apparently do not influence each other.

Platelet counts in blood from splenic vessels and spleen substance with note on heparin effect. ALFRED LEWIN COPLEY. *Division of Research Surgery, Dept. of Surgery and Gynecology, Univ. of Virginia School of Medicine, Charlottesville.* Blood samples were drawn within 20 minutes from the splenic artery and vein in 8 dogs under anesthesia, and by spleen puncture in 7 dogs. Blood was mixed immediately with Aynaud solution, and with 1 and 10 colorimetric units (Copley-Whitney, J. Lab. Clin. Med. **29**: Jan., 1944) of sodium heparin (Abbott) in saline. The action time of heparin was 15 minutes. The Copley-Robb method with 0.5 per cent solution of brilliant cresyl blue (National Aniline NV-27) was used and the platelets counted in all 25 squares of the Neubauer chamber were multiplied by 1,000.

The heparin effect of platelet count decrease (Copley-Robb, Am. J. Clin. Path., **12**: 416, 1942) in the splenic vessels was: 1 unit, 9–60 per cent; 10 units, 24–64 per cent. With 1 unit, 3 spleen samples showed no decrease, but 4 spleens 31–51 per cent. With 10 units, the decrease was 9–61 per cent.

Counts in 6 arteries were 10–31 per cent lower, and in 2 arteries 12 and 18 per cent higher than in the veins. Splenic artery and spleen showed in 2 cases the same count; in 1 case, 30 per cent higher in the spleen; in 4 cases, 30–50 per cent lower in the spleen. Comparative counts between splenic vein and spleen showed small increase of 11 per cent in 2 spleens; however, the count was in 5 cases 28–55 per cent decreased in the spleen. Results suggest that platelets are destroyed, and may be stored or formed in the spleen.

The effects of insulin hypoglycemia on the glycogen content of the various parts of the central nervous system of the dog. ANNETTE CHESLER (by invitation) and HAROLD E. HIMWICH. *Dept. of Physiology and Pharmacology, Albany Medical College, Union Univ., Albany, N. Y.* The glycogen contents of the various parts of the central nervous system have already been determined in dogs and cats with normal levels of blood sugar. It was found that each portion of the central nervous

system contained a characteristic concentration of glycogen, and, in general, in the adult this concentration followed a definite order, being most scarce in the cord and growing ever larger in the succeeding rostral layers from the cord. In the present experiments the glycogen contents of all parts of the central nervous system were examined in an effort to correlate the changes in the various parts with the duration of intense hypoglycemia.

The observed decreases in glycogen concentrations did not take place in a haphazard fashion, but in a definite order, which with the one exception of the cerebral cortex, extends from a rostral to a caudal direction. [*Aided by a grant from the Scottish Rite Fund.*]

Activity in the great superficial petrosal nerve influencing the electroencephalogram. CHESTER W. DARROW, JOHN B. GREEN (by invitation) and WARREN S. MCCULLOCH. *Inst. for Juvenile Research and Depts. of Neurology, Neurological Surgery and Psychiatry, Univ. of Illinois College of Medicine, Chicago.* Since the least complicated portion of the parasympathetic path to the cerebral blood vessels is the great superficial petrosal nerve, it was exposed subtemporally and its activity recorded synchronously with the EEG of both hemispheres, the EKG and the alterations in blood pressure.

Following section of this nerve peripherally to the electrodes high potential hypocapnic slow waves in the EEG were enhanced, but the operation caused no significant change in the activity recorded from the proximal stump.

The waves recorded from it fall into two ranges of frequencies. The lower frequencies, 8–15 per second, decreased in amplitude with increase of blood pressure and slowing of pulse, and bursts of this frequency often anticipated or accompanied slow waves in the EEG. Technical difficulties make it impossible to state whether these presumably sympathetic impulses were of local or extraneous origin.

The higher frequencies recorded from the nerve, 24 or more per second, increased in amplitude with each pulse, and in amplitude and frequency during sustained rise of blood pressure—thus resembling those recorded by Bronk and Stella from the carotid sinus. These changes often anticipated or accompanied increased frequency and regularity of the EEG.

These autonomic impulses may exert an influence on the activity of brain.

Cholinergic influence on high potential slow waves of the electroencephalogram. CHESTER W. DARROW, JOHN R. GREEN (by invitation), EDWARD W. DAVIS (by invitation) and HUGH W. GAROL (by invitation). *Inst. for Juvenile Research and Depts. of Neurology, Neurological Surgery and Psychiatry, Univ. of Illinois College of Medicine, Chicago.* That alkalinity increases the destruction of acetylcholine may explain why it is only during hypocapnia that there is concurrence of cardiac acceleration and slow waves in the EEG, and why only under hypocapnia the effects of section of the parasympathetic path in the facial nerve become apparent in the EEG. If this is the case protection of acetylcholine by physostigmine should prevent slow waves during hypocapnia, and atropine should produce them with little or no hypocapnia.

This was tried before and after section of the facial nerve in cats under B-erythroiden with artificial respiration. The results confirmed the hypothesis.

Effect of soybean lecithin upon the red blood cell count of normal dogs. JOHN EMERSON DAVIS. *Dept. of Physiology and Pharmacology, Univ. of Arkansas, Little Rock.* We have previously reported that liver, choline, certain vasodilator drugs, and soybean lecithin are capable of depressing experimental polycythemia in dogs or rabbits. Most of these substances have been shown to have no effect upon the normal erythrocyte numbers when fed to normal animals daily for a period of one week in the doses which are effective in depressing polycythemia.

In order to see whether a more prolonged period of feeding would affect the red blood cell counts, we have administered five grams of soybean lecithin daily to four normal dogs for two to three weeks. This procedure caused no changes in erythrocyte counts or hemoglobin percentages during the first week, but within two weeks significant reductions in red cell count were apparent in all dogs. The average reduction in erythrocyte number was 16 per cent (range 12 to 19 per cent). Mean arterial blood pressure determinations are being made but results are as yet inconclusive. These experiments are still in progress.

Stimulation of the red bone marrow by fat ingestion in anemic dogs. CHARLES DUPEE (by invitation), VICTOR JOHNSON, ALBINO MARCHELLO (by invitation) WARREN WILNER (by invitation) and L. WILLARD FREEMAN (by invitation). *Dept. of Physiology, Univ. of Chicago.* Previous reports from this laboratory indicate that in dogs, a high fat diet increases the rate of normal daily erythrocyte destruction, but that such a diet does not produce anemia, presumably because the red bone marrow can compensate for these extra losses.

To determine whether the hyperactive bone marrow in anemia can also cope with these losses, four dogs were fed a high fat diet and four a low fat diet of the same caloric value per kilogram body weight. All animals were kept anemic for 4 to 6 months by repeated bleedings, which were of equal magnitude for each pair of animals consisting of a control and an experimental dog.

In the fat fed dogs there were only some sugges-

tions that the anemia was more severe, and recovery from the anemia delayed. However, autopsy examinations of the femurs revealed a more active and more extensive red bone marrow in the fat fed animals, indicating that a high fat diet taxes the hematopoietic activity of the bone marrow more than does a low fat diet, in the recovery from hemorrhagic anemia.

Several physiological functions during rest and exercise in normal subjects, patients with pulmonary silicosis, and patients with pulmonary siderosis. NORBERT ENZER (by invitation) and ERNST SIMONSON. *Research Laby., Mount Sinai Hospital, Milwaukee.* In a group of normal subjects (varying from 8 to 100 for different functions), 15 patients with siderosis (deposition of iron in the lungs without fibrosis, but with x-ray pictures similar to those in silicosis) and 8 patients with silicosis, the following functions were investigated: endurance in dynamic work (lifting loads) and static work; muscle strength in backmuscles, arm extensors and handgrip; pulse rate during and after dynamic and statis exercise; fusion frequency of flicker during rest and after exercise; maximum tapping rate; vital capacity; minute pulmonary ventilation at rest in sitting and standing position, during and after dynamic and static exercise; maximum voluntary pulmonary ventilation; relative pulmonary reserve (maximum ventilation minus highest minute volume during exercise); coefficient maximum pulmonary ventilation: vital capacity; coefficient excess ventilation: m-kilo dynamic exercise; coefficient excess ventilation per second static exercise. No statistically significant difference between the normal group and the siderosis group was found in any function while the silicosis group showed significant depression of vital capacity, maximum pulmonary ventilation, relative pulmonary reserve, endurance in dynamic and static work. A far greater percentage of patients with silicosis than of patients with siderosis showed an individually significant depression of functions compared to the normal limits.

The effect of electric shock therapy on gastric contraction and gastric secretion. DOROTHY FETTER (introduced by Helen Coombs). *New York State Psychiatric Inst., New York.* During electric shock therapy, fifteen psychotic patients were studied to find what effect electric stimulation might have upon the stomach movements. While the patient underwent a grand mal seizure as a result of having an electric current passed through the head, changes in intragastric pressure were recorded by the balloon method. A rise in intragastric pressure lasting thirty to forty seconds immediately followed the application of shock. In most cases a second rise of pressure followed the first and lasted seven to forty-eight seconds. During the seizure, a pneumograph recorded the contraction of the abdominal muscles. Because the twitchings of these muscles and the recorded rise of intragastric pressure were not synchronous, it was assumed that the increase was due to contraction of the stomach wall. This might have been due to vagus stimulation.

In fourteen psychotic patients with low fasting gastric juice acidity, nine showed an increase in secretion of acid gastric juice following the induction of a grand mal attack by electric shock therapy. The average increase for free acid was from 0 to 25, and the total acid increase was from five to forty. The figures represent cubic centimeters of 1/10 normal NaOH necessary to neutralize 100 cc. gastric juice. In five such patients no significant change occurred. The increase in secretion and acidity which followed application of electric shock in the majority of the patients implies activity of the vagus nerve as a result of the therapy.

The effects of nicotine on urinary secretion. ERNST FISCHER. *Dept. of Physiology, Medical College of Virginia, Richmond.* In dogs, in dial or ether narcosis, blood pressure and secretion rate of the urine and its electric conductivity were recorded continuously. The blood pressure effect of nicotine can be triphasic. The middle phase, the main effect, is the increase in pressure, which is not affected by the choice of the anesthetic. The first phase, an initial drop, is suppressed by ether. The third phase, a secondary drop not affected by the anesthetics, occurs only after large doses. The renal effect is not distinctly influenced by anesthetics but is dependent on the functional state of the kidneys. The effect is practically nil for poorly secreting kidneys. If the kidneys are forming urine at a moderate rate, this rate will be increased by nicotine after the blood pressure has returned to normal level. This increased secretion which after large doses lasts for more than half an hour, is not accompanied by distinct changes in electrolyte concentration. During water or caffeine diuresis, the nicotine effect is expressed much more by an increased electrolyte content than by an increase in volume. During Nacl or Na_2SO_4 diuresis, the nicotine effect is more or less suppressed, probably because the kidneys are already performing maximal work.

The straight part of the curve showing the relation between magnitude of effect and log of the nicotine doses has a much steeper slope for the blood pressure increasing effect than for the diuretic effect. This might suggest that the latter is completely independent of the former. However, if in analogy to LD_{50} that dose is calculated which will produce 50% of the maximal possible effect, it becomes evident that this dose is about the same for both effects.

The birefringence of striated and smooth mam-

malian muscles. ERNST FISCHER. *Dept. of Physiology, Medical College of Virginia, Richmond.* The birefringence of isolated living fibers of mammalian skeletal muscles (dog, rabbit, cat, mouse) is somewhat greater than the values reported for frog muscles. In twenty experiments, in which the birefringence of the whole rectus abdominis of small mice was determined at maximal natural length and for 10 and 20% stretch, the mean values were (expressed in 10^{-3} mm. phase difference per mm. thickness) 2.62 ± .02, 2.68 ± .02, and 2.72 ± .03 respectively. In contrast to the marked effect of stretch upon the birefringence of smooth avertebrate muscle, this increase is rather small for skeletal muscle as was demonstrated also on isolated fibers fixed in formalin at various lengths. Analysis of the birefringence of the fixed fibers of various muscles with the method of Noll and Weber revealed that, as in striated frog muscle, the refractive index of the extracellular phase is 1.55 and that 70% of the total birefringence is due to form birefringence and 30% due to crystalline birefringence. No difference in birefringence exists between striated fibers of the oesophagus and true skeletal muscles.

Corresponding analysis for mammalian smooth muscles (retractor penis, intestinal muscular coats) demonstrated that birefringence increases continuously and at a high rate with stretch. The ratio between form and crystalline birefringence is smaller than for striated muscles, but not so low as for smooth avertebrate muscles. The refractive index of the extra-micellar phase of 1.53 is just between 1.51 as found for smooth avertebrate muscle and 1.55 as found for vertebrate striated muscle.

The protection against serine injury by dietary factors, especially pyridoxine. WILLIAM H. FISHMAN and CAMILLO ARTOM (introduced by Arthur Grollman). *Dept. of Biochemistry, Bowman Gray School of Medicine, Winston-Salem, N. C.* It has been previously shown by us (J. Biol. Chem. **145:** 345, 1942) that a high mortality, accompanied by demonstrable pathological lesions occurs following serine administration by stomach tube in rats maintained on an experimental and not in those on the stock diet. In the present experiments, a similar synthetic diet has been employed, except that B-vitamins were omitted.

When serine was given parenterally, effects similar to those obtained by stomach tubing were observed. On the other hand, the same amount of serine mixed in the diet was harmless. It is suggested that the ratio between the rates of absorption and elimination of the aminoacid is an essential factor in the production of the injury.

A high degree of protection against the injurious action of serine comparable to that in rats on the stock diet is obtained by the addition to the diet of choline, cystine and glycine, together with the injection of a mixture of most of the known B-vitamins. When these substances were tested individually, only pyridoxine exerted a significant protective action. Therefore, it is tentatively syggested that pyridoxine may be involved in some phases of the metabolism of serine. [*Aided by a grant from the John and Mary R. Markle Foundation.*]

Studies on the hypercholesterolemia of immature fowl induced by estrogens. WALTER FLEISCHMANN and ILSE A. FRIED (by invitation). *Dept. of Pediatrics, John Hopkins Univ. School of Medicine.* Total body cholesterol and serum cholesterol were determined in immature chickens of both sexes treated with estradiolbenzoate and in untreated controls. The average serum cholesterol of the treated birds was 267 ± 48 mg. %; that of the untreated controls 114 ± 21 mgm. per cent. The average cholesterol content of the exsanguinated bodies was 0.19 ± 0.01 per cent of bodyweight for both groups. These data indicate that estradiol influences the shift of cholesterol from the tissues to the blood plasma. It has been shown previously in rodents that thyroxine influences the shift of cholesterol from the blood plasma to the tissues. (Fleischmann and Shumacker, Bull. Johns Hopkins Hosp. **71:** 175, 1942). It was therefore assumed that thyroxine and estradiol influence the distribution between blood plasma and the tissues in opposite directions. In accordance with this theory it was found that the hypercholesterolemia produced in birds by injection of 1 mg. estradioldipropionate daily could be inhibited completely by simultaneous administration of 1 mg. of thyroxine daily. The levels of calcium in the serum follow the trend of serum cholesterol closely. As an example, the data of one representative experiment on three immature roosters are given: Untreated control: serum cholesterol 112 mgm. per cent Ca 10.7 mgm. per cent. Bird treated with 1 mgm. of estradioldipropionate intramuscularly daily through five days: serum cholesterol 251 mgm. per cent, Ca 41.3 mgm. per cent: Bird treated with 1 mg. thyroxine subcutaneously daily in addition to the same dose of estradioldipropionate: serum cholesterol 112 mgm. per cent, Ca. 11.5 mgm. per cent. [*Aided by a grant from the Commonwealth Fund. The hormones were kindly supplied by Roche-Organon Inc., Nutley, N. J.*]

Radioactive phosphorus uptake in the liver, kidney and intestine of the mouse. R. PHYLLIS FOX (by invitation) and CHARLES D. KOCHAKIAN. *Dept. of Vital Economics, Univ. of Rochester, Rochester, N. Y.* A study was made of the effect of castration and testosterone propionate administration on the soft tissues of mice of the dba strain.

At the age of one month, animals were divided into four groups as follows: (a) normal (b) castrate (c) normal implanted with pellet of testosterone

propionate (d) castrate implanted with pellet of testosterone propionate.

After 5, 7, and 9 months, animals from each group were sacrificed for the determinations.

Twenty-four hours before sacrifice, radioactive phosphorus was injected intraperitoneally as disodium phosphate.

As shown by P^{32} determinations, the uptake of PO_4 by the liver was unaffected by castration or hormone administration. The kidney was similarly unaffected. In the case of the intestine, however, a marked depression of the uptake occurred at 7 months in castrated animals as compared with normal mice. This effect depended on the time of castration of the animals.

The effect of castration and testosterone propionate administration on the phosphorus metabolism of the pelves and femurs of the mouse as determined by radioactive phosphorus studies. R. PHYLLIS FOX (by invitation) and CHARLES D. KOCHAKIAN. *Dept. of Vital Economics, Univ. of Rochester, Rochester, N. Y.* Mice of the Murray-Little dba strain were divided into four groups as follows: (a) normal (b) castrate (c) normal implanted with pellet of testosterone propionate (d) castrate implanted with pellet of testosterone propionate. Castration and implantation was done at one month of age. Animals from each group were killed by decapitation after 5, 7, 9 months. Twenty-four hours before autopsy radioactive phosphorus was injected intraperitoneally as the disodium phosphate. After fat extraction and glycol ashing, the uptake of P^{32} by the femurs and pelves was measured in the usual manner.

The femurs and pelves of the castrated mice contained more radioactive phosphorus than those of the normals, whereas the femurs of the treated mice showed values similar to those of the normals. These effects were found at 5, 7 and 9 months.

The femurs and pelves of the castrated mice were longer than those of the normals, while the latter, in turn, were longer than those of the treated animals.

There was no difference in either ash content or calcium and phosphorus content as a result of castration or hormone administration.

The utilization of sodium iron pyrophosphate by anemic rats. SMITH FREEMAN and M. W. BURRILL (by invitation). *Dept. of Physiology, Northwestern Univ. Medical School, Chicago, Ill.* A difference of opinion exists regarding the utilization of sodium iron pyrophosphate by anemic rats. The question is of considerable importance inasmuch as this compound is used for enriching white flour. To study this question rats were made anemic according to the technique of Elvehjem and Kammerer. The depleted rats were divided into two groups of 10 each, comparable as to sex, litter, weight and hemoglobin. Both groups received 0.25 mg. of iron daily, one as ferric chloride and the other as sodium iron pyrophosphate; also supplements of copper and manganese.

The initial hemoglobin values per 100 cc. were 3.07 gm. and 3.04 gm. for the ferric chloride and pyrophosphate groups respectively. After 28 days on the iron supplements the average hemoglobin values were 13.72 gm. for ferric chloride and 7.80 gm. for pyrophosphate. The hemoglobin increase for the pyrophosphate was therefore 44.6 per cent that of the ferric chloride group.

The average total iron content of the carcass was 5.83 mg. for ferric chloride and 3.25 mg. for pyrophosphate. The average iron content of a depleted rat is approximately 1 mg. Correcting the final iron content for this amount, the percentage of ingested iron retained was 69 per cent for ferric chloride and 32 per cent for sodium iron pyrophosphate.

Under the conditions of this experiment the utilization of sodium iron pyrophosphate was a little less than half that of the ferric chloride iron. [*This study was assisted by a grant from the Victor Chemical Works.*]

Seasonal changes in water content and oxygen consumption in brain of the black bass. FREDERICK A. FUHRMAN (by invitation) and JOHN FIELD 2D. *Dept. of Physiology, Stanford Univ.* The influence of temperature on the metabolism of the excised brain of the black bass (*Huro salmoides*) was described previously (Physiol. Zool., in press). These measurements were made on summer fish (habitat temperature 22°–24°C). To ascertain whether the effect of temperature on the oxygen uptake of this tissue would vary with season, a similar study has now been made on the brain of the same species taken during the winter (habitat temperature 12° to 16°C).

On a wet weight basis the Qo_2 of the brains of the winter fish (similar body sizes) averaged about 20 per cent higher than the Qo_2 of the brains of summer fish over the range 10° to 30°C. The mean water content of the brain of the summer fish was 82.23 per cent, that of the winter fish was 79.59 per cent (10 determinations on each). The difference between these means is sgnificant ($P = 0.001$). If the Qo_2 is calculated on a dry weight basis there is no significant difference in Qo_2, at corresponding temperatures, between the brains of winter and summer animals of this species. [*Supported in part by a grant from the Markle Foundation.*]

Influence of temperature on the respiration of excised rat ventricle tissue. GERALDINE J. FUHRMAN (by invitation) and JOHN FIELD 2d. *Dept. of Physiology, Stanford Univ.* Few values of the oxygen consumption of isolated cardiac tissue appear in the literature and these few indicate considerable variability even between samples taken from

one animal. The Qo_2 is rather low, ranging from 0.6 to 7.4 (dry weight basis).

In our experiments ventricular tissue (rat) was sliced to a thickness of about 0.2 mm. using a lucite template and razor. Oxygen consumption was measured by the direct method of Warburg. The liquid and gas phases were Ringer's-glucose-phosphate and oxygen respectively. The results of measurements made at graded temperatures are given in the following table.

Temperature (°C.)	10°	15°	20°	25°	30°	35°	37.5°	40°
No. of animals	3	3	3	3	7	5	17	3
Mean Qo_2 (dry)	0.9	2.0	3.2	5.2	6.8	8.4	10.4	8.35

At 37.5°C the mean Qo_2 of samples from 17 animals was 10.4. The standard error of the mean was 0.13. The graph obtained when mean Qo_2 was plotted as a function of temperature in general resembled similar curves for other tissues. However, under the conditions of these experiments Qo_2 was not a linear function of temperature (centigrade) and log Qo_2 was not a linear function of either centigrade temperature or of the reciprocal of the absolute temperature over any considerable range. In these respects the Qo_2 temperature curve resembles the frog heart rate-temperature described by A. J. Clark (1920). [*Supported in part by grants from the Markle Foundation and from the Fluid Research Fund, Stanford Medical School.*]

The effect of thyroxin on water diuresis and water intoxication in the rat. ROBERT GAUNT. *Dept. of Biology, Washington Square College of Arts and Science, New York Univ., New York, N. Y.* Hyperthyroidism was produced in rats by the administration of 0.2 mg. thyroxin daily for about three weeks. These animals showed a daily water intake and urine output approximately 100% above normal.

They also showed after fasting an increased diuretic response to water given either in small or large doses by stomach tube. A striking protection against the lethal effects of water intoxication resulted.

Water intoxication was produced in normal rats by the administration of 13 doses of water at half-hour intervals. The dose was 3 cc per 100 sq. cm. of body surface (this approximates 5% of the body weight). Severe intoxication symptoms always resulted and death occurred in about 60% of the cases.

Hyperthyroid rats, given the same amounts of water, were markedly resistant to all of the symptoms of water intoxication (see above abstract) and the occasional deaths were apparently due to other causes (cardiac failure?). Most notable, perhaps, was the ability of hyperthyroid animals to excrete tremendous volumes of water of low chloride content, thus maintaining their plasma levels of this ion.

The protective action of thyroxin was largely abolished by adrenalectomy. The intense adrenal cortical stimulation induced by thyroxin, however, probably does not account for all of the effects on water metabolism. [*Aided by a grant from the Josiah Macy, Jr., Foundation.*]

Water diuresis and water intoxication in relation to the adrenal cortex. ROBERT GAUNT. *Dept. of Biology, Washington Square College of Arts and Science, New York Univ., New York, N. Y.* After adrenalectomy diminution in water diuresis occurs with a susceptibility to water intoxication. This appears within 18 hours and becomes more severe later even in animals maintained on cortical hormones or salt. One day after adrenalectomy rats respond readily to replacement therapy; later the response is erratic.

The diuretic response to intraperitoneal saline solutions is also subnormal after adrenalectomy.

Two separable factors cause the lack of water diuresis in adrenalectomized rats: 1, a delayed intestinal absorption and emptying of the stomach; and, 2, an inability to excrete water that is absorbed.

Normal rats can be protected from lethal water intoxication by cortical hormones.

Adrenalectomized rats show a sharp rise in hematocrit, some elevation of hemoglobin, and a severe fall in plasma chloride and protein after even small doses of water. The urine chloride loss is small and the plasma drop is due partly to a shift to the gut.

The terminal hematocrit rise in both normal and adrenalectomized rats is such as to suggest erythrocyte swelling. The fall of plasma chloride is less in normal than in adrenalectomized animals, although the urinary loss is greater. The blood sugar rise in normal rats is due to adrenal medullary activity.

Blood pressure is well maintained in both normal and adrenalectomized rats.

Body temperature falls sharply giving an excellent measure of the extent of water intoxication in both normal and adrenalectomized rats. [*Aided by a grant from the Josiah Macy, Jr., Foundation.*]

The effect of hypertensin in renal hypertensive dogs. M. L. GOLDBERG (by invitation) and G. E. WAKERLIN. *Dept. of Physiology, Univ. of Illinois College of Medicine.* Previous reports from our laboratory have dealt with the antipressor effect of daily intramuscular injections of hog kidney extracts containing renin in renal hypertensive dogs. Since the antirenin produced by these injections does not appear to constitute the mechanism of the antihypertensive effect, we investigated the possibility that an "antihypertensin" might be involved. Since hypertensin is probably a polypeptide, its ability to produce an "antihypertensin" was questioned but vasopressin which is a

polypeptide has been shown to give rise to an "antivasopressin" (Am. J. Physiol., **133**: P. 341, 1941).

Accordingly hypertensins were injected intramuscularly into eight renal hypertensive dogs, in a dose of two units per Kg. daily for five months (one unit giving a 25–30 mm. rise in blood pressure in a 10 Kg. dog). Each pair of animals received a different hypertensin (prepared according to the method of Houssay and his group) i.e., two dogs received hypertensin prepared by incubating hog renin with hog serum hypertensinogen, two dogs received hypertensin prepared by incubating dog renin with dog serum hypertensinogen, and the remaining two pairs were given hypertensins prepared by incubating dog renin with hog serum hypertensinogen and by incubating hog renin with dog serum hypertensinogen, respectively.

No significant change in the blood pressure was noted in the eight dogs during or following the daily injections of the hypertensins. Assays of the serums of the dogs during and after the hypertensin injections failed to reveal the presence of "anti-hypertensin," which was likewise true for hypertensive dogs successfully treated with hog renal extract containing renin.

The results suggest that the antihypertensive effect of hog renal extracts containing renin does not operate through a hypertensin-antihypertensin mechanism. [*Aided by a grant from the John and Mary R. Markle Foundation.*]

Effects of thiourea administered to mothers on the thyroid gland of the suckling rat. E. D. Goldsmith (by invitation), Albert S. Gordon and Harry A. Charipper, *Dept. of Biology, Washington Square College of Arts and Science, New York Univ.* Rats, suckled by mothers maintained on a laboratory stock diet containing 0.5% thiourea, were sacrificed at periods varying from 4 to 24 days after birth. The thyroids of these young rats were found to be hyperemic and enlarged. The degree of hyperplasia varied directly with the duration of treatment. Representative cases are shown in table 1. Control rats from untreated mothers possessed considerably smaller glands (e.g., 17–18 gram rats, 3 mgm. thyroids; 45 gram rats, 5.0 mgm. thyroids).

TABLE 1

Litter no.	Pre-partum treatment (in days)	Post-partum treatment (in days)	Weight of animal (in gm.)	Weight of thyroid (in mgm.)
1a	4	8	17	5.0
1b	4	11	21	7.5
1c	4	15	37	10.0
2	5	19	30	10.0
3	0	10	16	5.5
4a	0	21	30	14.0
4b	0	24	38	21.0

The relative importance of the pre- and post-partum periods in the production of this thyroid hyperplasia in suckling young, and whether or not the enlargement is brought about by the thiourea directly or through the action of the thyrotropic hormone of the mother are being investigated.

Rate of disappearance of pregnant mare serum gonadotropin injected into the rat. Albert S. Gordon. *Dept. of Biology, Washington Square College of Arts and Science, New York Univ.* The antihormone technique of Zondek, Sulman and Sklow (J. Endocrinology, **2**: 1941, 362) was employed in determining the rate of disappearance of pregnant mare serum hormone following a single injection. Each of 150 immature female rats was given a subcutaneous injection of 10 Cole-Saunders units of a highly purified pregnant mare serum gonadotropin. These animals were then divided into 5 groups and the rats of each group injected subcutaneously with varying quantities of antihormone serum 1, 5, 12, 24 and 36 hours after administration of the gonadotropin. All rats were sacrificed 6 days after injection of the hormone and the ovarian weights recorded. The antihormone serum was highly potent and was obtained from rabbits injected with the purified pregnant mare serum gonadotropin for 5 months. Using the magnitude of the ovarian weights as the criterion, it was found that there was little change in the value of the minimal amount of antiserum required to abolish the effects of the hormone up to 24 hours after injection of the gonadotropin. Beyond this time (i.e., 36 hours) the method is not applicable since now the antihormone is ineffective in preventing the gonadotropic action.

These results would seem to indicate that no appreciable decrease in the amount of physiologically active pregnant mare serum gonadotropin occurs in the organism for at least 24 hours following its injection. On the other hand, it has been shown that chorionic gonadotropin (P.U.) suffers at least a 50 per cent decrease in activity 1-4 hours after its injection (Zondek et al.). [*Thanks are extended to Dr. Erwin Schwenk, Schering Corporation, for the supply of purified pregnant mare serum hormone.*]

Effect of organs on the activity of thyrotropic hormone. Albert S. Gordon, Savino A. D'Angelo[1] (by invitation) and Harry A. Charipper. *Dept. of Biology, Washington Square College of Arts and Science, New York Univ.* Thyrotropic hormone (antuitrin T), dissolved in isotonic Brinkman's buffered solution, was incubated with slices of various organs at 38°C. At the end of 2 hours, the materials were centrifuged and the supernatant fluids assayed for thyrotropic hormone content in 340 young Fana pipiens larvae

[1] Now Aviation Physiologist, MacDill Field, Tampa, Florida.

according to the method of D'Angelo, Gordon and Charipper (Endocrinology, **29**, 1942, 217). All tadpoles received 7 injections of 0.05 cc of the fluids pleuroperitoneally over a period of 14 days. Using the rate of hind limb growth, body weight loss, and time of forelimb extrusion as criteria, a definite augmentation of the thyrotropic hormone activity was observed with both liver and kidney. In one experiment this augmentation amounted to approximately 400 per cent. Skeletal muscle was without effect; small intestine always produced inhibition of the thyrotropic hormone.

These organs have already been reported to exert substantially similar effects on the activity of pregnant mare serum gonadotropin (Gordon and Levenstein, Anat. Rec., 1941, **81**, 100).

Relation of electroencephalographic effects of hyperventilation to parasympathetic function. JOHN R. GREEN (by invitation), CHESTER W. DARROW, EDWARD W. DAVIS (by invitation) and HUGH W. GAROL (by invitation). *Depts. of Neurology, Neurological Surgery, and Psychiatry, Illinois College of Medicine, and Institute for Juvenile Research, Chicago.* Association of high potential slow waves with increased heart rate induced by hyperventilation suggested that inhibition of parasympathetic activity might affect the brain. This was tested by section of the parasympathetic pathway over facial nerve, geniculate ganglion, great superficial petrosal and internal carotid nerves.

The geniculate ganglion of the facial nerve was exposed in cats under ether. Animals were then curarized with B-erythroiden and given artificial respiration. After section of one or both facial nerves the high potential slow activity precipitated by two minutes of hyperventilation was greatly exaggerated. Stimulation of the peripheral cut nerve ends reduced or prevented the slow waves. Two animals failed to produce slow waves after both nerves were cut, suggesting irritation at the cut ends, and when these were injected with alcohol, hyperventilation produced typical slow waves in the EEG.

Hence, parasympathetic impulses via the facial nerve counteract the alteration of cortical activity produced by effects of hypocapnia.

A respiratory reflex response to cold in the goat. ALBERT J. GREENBERG (by invitation), WILLIAM E. PETERSEN (by invitation) and M. B. VISSCHER. *Depts. of Physiology and Dairy Husbandry, Univ. of Minnesota.* The goat and other ruminants held at ordinary room temperatures in the dorsal recumbent position regularly show increased rates of breathing. The respiratory rate rises from 15 per minute at the outset, to 100 to 150 per minute after one to five hours in the position described, when the animal is kept in a room at 20°C or above. This response has been observed in each of seventeen animals so treated. In four cases, after extreme polypnea had developed and been maintained for an hour or more, the animal was exposed to a temperature approximately 0°C. In each instance there was a prompt drop in respiratory rate, reaching 30–40 per minute within an hour. This response may be mediated through a vasomotor reflex reaction to cold. A second series of experiments showed that massive intravenous infusion of physiological saline solution produces a similar fall in respiratory rate in goats showing the above-described postural polypnea. The circulatory embarrassment caused by maintenance of the dorsal recumbent posture in ruminants has been discussed previously. [*Greenberg, Visscher, Petersen and Boyd*; *J. A. Vet. Assoc.* **101**, 417, 1942.]

Adrenocortical-like tissue in the ovaries of the adrenalectomized ground squirrel. R. A. GROAT (introduced by W. F. Windle). *Inst. of Neurology, Northwestern Univ. Medical School, Chicago.* Lessened food intake and inability to survive a fast are criteria of two different levels of adrenal insufficiency in the adrenalectomized ground squirrel. Adrenalectomy is fatal in most instances, but if the operated animal drinks 1% sodium chloride solution, its food intake is maintained and it survives. At a variable time after adrenalectomy (minimum, 15 days for the female) 1% sodium chloride solution can be replaced by water and the animal will continue to eat. Later, 3 or 4 months after operation, it will survive a fast. The gradual adjustment in response to removal of the adrenals has been shown to be formation of adrenocortical-like tissue in the animal. This tissue grows most readily in the ovaries.

Cells functionally and morphologically like those of the adrenal cortex invariably develop in the ovaries of the young and the mature adrenalectomized ground squirrel. These adrenocortical-like cells arise by metaplasia from stromal cells in the ovaries and from mesenchymal-like periepoophoron cells in the mesovaria. Eventually sufficient adrenocortical-like tissue accrues to maintain the animal in a normal state.

The physiological evidence for the identity of the adrenocortical-like cells is threefold. First, the tissue was found in the ovaries of all adrenalectomized ground squirrels but not in the ovaries of any intact animals. Secondly, removal of the hypophysis prevented appearance of adrenocortical-like cells in the ovaries after adrenalectomy. Thirdly, the state of adrenocortical insufficiency ameliorated as the amount of adrenocortical-like tissue in the ovaries increased.

Functional alterations in motor and supranuclear mechanisms in experimental concussion. R. A. GROAT (by invitation), H. W. MAGOUN, F. L. DEY (by invitation) and W. F. WINDLE. *Inst. of Neurology, Northwestern Univ. Medical School,*

Chicago. Concussion was produced by applying adequate force to the cat's brain by means of a pendulum striking the head or by means of an hydraulic system connected with the interior of the cranium. Respiration ceased; the canthus, pupillary-light, startle and pinna reflexes disappeared; the pupils dilated and the nictitating membrane retracted. Electrical stimulation within the brain by means of fine electrodes placed with the Horsley-Clarke instrument revealed that excitability of the intra- and extra-cranial portions of the cranial motor nerves and of the descending fibers from the cerebral cortex in the basis pedunculi were unimpaired in concussion. Excitability of nerve-cell groups comprising cranial motor nuclei was impaired less frequently, to a smaller degree and for shorter intervals than excitability of supranuclear motor parts, such as brain-stem tegmentum, hypothalamus and motor cortex. The inspiratory center of the medulla oblongata behaved much like a cranial motor nucleus. Cessation of respiration and abolition of reflexes appeared not to be motor defects. Concussional alterations in function set in at the moment concussion was produced and functional recovery occurred gradually. A brief, often momentary, excitatory effect on motor neurons, apparently correlated with decreased thresholds, was sometimes observed upon concussion. [*The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Northwestern Univ.*]

The reduction of blood pressure in experimental hypertension by the administration of oxidized marine oils. ARTHUR GROLLMAN. *Dept. of Medicine, Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C.* In confirmation of our earlier reports (Proc. Soc. Exper. Biol. and Med. **52**: 162, 1943; Fed. Proc. **2**: 81, 1943) the oral administration of various marine oils after mild oxidation results in a reduction of the blood pressure of hypertensive animals (rats, dog). About 30 commercially available marine oils have been compared as regards their efficacy, which varies widely in oils of diverse origin. Oils derived from the basking shark's liver, the cod's liver, and sardine body oil have proved to be most efficacious. Oil derived from a fresh-water species (the burbot) was inactive. By chilling the crude oils and centrifuging at 5° to 10°C, it is possible to effect an approximately three-fold concentration of the active principle. Fractionation between aqueous alcohol and petroleum ether effects a further concentration. Preliminary chemical studies point to the active principle as being an oxidation product of a fatty acid. There is no correlation between the original vitamin A content of the various oils tested and their potency as regards their capacity to reduce blood pressure following oxidation. [*Aided by grants from the John and Mary R. Markle Foundation and from Mr. Joe Wethan.*]

The effect of jejunal pedicle grafts and perfusion with jejunal washings on the secretion of acid by the total stomach pouch of the dog. M. I. GROSSMAN (by invitation), HARRY GREENGARD, JEAN REA WOOLLEY (by invitation) and A. C. IVY. *Dept. of Physiology, Northwestern Univ. Medical School, Chicago.* Andrus et al. (Annals Surg., **118**: 499, 1943) have reported that implantation of a jejunal graft with intact pedicle into the wall of the stomach produces a reversal of the normal response of the gastric glands to histamine stimulation, i.e., histamine causes a decrease in acid secretion by the stomach. This same report states that acid concentration in response to histamine stimulation is depressed by placing saline washings of a Thiry loop of jejunum into the stomach and allowing it to remain in contact with the gastric mucosa for 10 minutes, removing the washings at the time of histamine injection.

The present experiments were designed to study these phenomena quantitatively by the use of dogs with pouches of the entire stomach. In two such animals a segment of the first loop of jejunum 6–8 cm. long was resected, opened along its antimesenteric border and sewn into a gastrotomy. The pedicle of the jejunal segment was permitted to remain intact and in one case its integrity was proven by abdominal exploration one month after the original operation. Comparison of ten preoperative control histamine tests with ten tests on each animal performed 2 to 10 weeks postoperatively revealed no significant difference in the volume of secretion, concentration or output of free acid, or per cent of total acid occurring as free acid.

Fifty cc. of saline was perfused through the duodenum and first foot of jejunum in 5 dogs under nembutal anesthesia. Fifty cc. of the pooled jejunal perfusate was perfused through the total gastric pouch of each of 6 dogs for 20 minutes. Comparison of the response to histamine stimulation immediately after perfusion with control tests without perfusion revealed no significant deviations.

The phenomena reported by Andrus et al. for the *in situ* stomach of the dog could not be reproduced in the pouch of the entire stomach.

Gastric analyses on Mann-Williamson dogs following enterogastrone treatment. M. I. GROSSMAN (by invitation), HARRY GREENGARD, JEAN REA WOOLLEY (by invitation) and A. C. IVY. *Dept. of Physiology, Northwestern Univ. Medical School, Chicago.* It has been noted that Mann-Williamson dogs show a prolongation of the gastric secretory response to a 7 per cent alcohol test

meal manifested by a failure of acid concentration to return to the basal level for as long as from four to six hours. Mann-Williamson dogs which have been protected from ulceration by the daily administration of enterogastrone concentrates for a period of one one year do not develop ulcers following withdrawal of treatment when observed for as long as two and one half years. Observations on these animals is continuing. Alcohol test meals when administered to these "immune" dogs elicit the same response as that noted in normal, untreated, unoperated dogs in that the secretory response returns to the basal level by the end of two hours.

The mechanism of the prolonged response to alcohol in the untreated Mann-Williamson dog and its prevention by enterogastrone treatment is obscure. The beneficial effect of the upper intestinal musocal extract may possibly be due to some factor other than the specific chalone enterogastrone. [*This study was assisted by a grant from the Josiah Macy Jr. Foundation.*]

The efficiency of contraction of isolated muscle during post-tetanic enhancement. S. A. GUTTMAN (by invitation) and MCKEEN CATTELL. *Dept. of Pharmacology, Cornell Univ. Medical College, New York City.* The possibility that the enhanced twitch response following a tetanus might be related to an improvement in the efficiency of contraction, i.e. the proportion of chemical energy converted to mechanical potential, was studied in the isolated sartorius muscle of the frog (*Rana pipiens*).

Using an isometric technic with photographic recording for the tension (T) and a sensitive thermopile-galvanometer system for measuring the initial heat (H), the efficiency (T/H) was determined for individual twitches before tetanizing the muscle and in the period following.

During the post-tetanic period of enhancement of the response there was at first a small decrease in efficiency (about 10 per cent) followed by a change in the opposite direction to a value about 10 per cent above the pre-tetanic control. As the enhancement subsided the efficiency also returned to the pre-tetanic value. There was thus no regular relationship between the degree of enhancement and the efficiency, furthermore the T(H changes were small in relation to the increase in the mechanical response. These facts lead to the conclusion that the enhanced twitch tension following a brief tetanus cannot be explained on the basis of a greater utilization of the energy liberated.

Electromyography as a method for the determination of level lesions of the spinal cord. SAMUEL A. GUTTMAN and PAUL F. A. HOEFER (introduced by F. A. Mettler). *Dept. of Neurology, Columbia Univ. College of Physicians and Surgeons, and the Neurological Inst. of New York.* The method consists of a systematic exploration of resting striated muscles in man by means of coaxial needle electrodes. Spontaneous motor unit discharges may occur with or without atrophy of muscles when the spinal cord segments by which these muscles are supplied, are involved in structural level lesions, such as intra- and extramedullary tumors, herniation of intervertebral discs, cyst, myelomalacia and others. The recording instrument was a six-channel inkwriting oscillograph. Seventeen out of 24 lesions verified by operation, autopsy or roentgenographic studies were well localized by finding spontaneous motor unit discharges limited to the muscles innervated by the cord segments involved (14) or by coinciding upper levels (3) while motor unit discharges were found several segments below the verified lower boundary of the lesion. In one case the localization by electromyography indicated a level one segment below the verified level. In 4 cases motor unit discharges were found over too many cord segments (though including the correct level) to allow for precise localization. Two false localizations were made. The data compare favorably with the localizing value of clinical motor, sensory and roentgenographic data in the same series. The motor unit discharges are presumably the result of lesion or irritation (or both) of the anterior horn cell areas alone or in combination with the internuncial neurone and the motor roots.

The use of furmethide to test sweat secretion in man. SAMUEL A. GUTTMAN (introduced by F. A. Mettler). *Neurological Inst. of New York and Dept. of Neurology, Columbia Univ. College of Physicians and Surgeons, New York.* The use of drugs for the production of sweating has been limited chiefly to pilocarpine hydrochloride and mecholyl (acetylbetamethylcholine hydrochloride). This method is of value in demonstrating neural lesions, chiefly those involving peripheral nerves. Pharmacological doses of pilocarpine or mecholyl too frequently induce unpleasant side reactions.

Furmethide (furfuryl-trimethyl-ammonium iodide), a drug possessing parasympathomimetic action, was administered to 35 adult human beings by hypodermic injection of 5 mg. into the deltoid region on one or more occasions. The presence of sweating was indicated by the change in color of a starch-iodine mixture (Minor's method).

Furmethide was found to possess the following advantages over pilocarpine hydrochloride as a drug to test sweating in man:

1. Sweat response of the face, upper extremities, thorax and abdomen usually appeared within 2–5 minutes after hypodermic injection into the deltoid region. Response to pilocarpine (10–12mg. doses) was slower and in many instances there was no response.

2. Annoying side reactions following furmethide were rare and could be readily controlled with atropine sulfate. Side reactions following pilocarpine were most frequent, more annoying and less readily controlled by atropine sulfate.

Effects of blood pressure levels on intestinal motility. A. S. HAMILTON (by invitation), D. A. COLLINS (by invitation), and M. J. OPPENHEIMER. *Dept. of Physiology, Temple Univ. School of Medicine, Philadelphia, Pa.* Changes in intestinal motility were observed in intact, adrenalectomized, and nephrectomized dogs (chronic Biebl loops) subjected to prolonged, severe hypotension followed by re-injection of heparinized blood (pentothal-barbital or morphine-barbital anesthesia). Intestinal recording was made from a balloon passed through the incised loop to the proximal duodenum. Two-hour control periods preceded bleeding.

Initial blood loss of 20 cc. per kg. rarely influenced tonus or peristalsis. Sharp reductions in tonus occurred when pressure reached 54-84 mm. At approximately 40 mm. peristalsis was usually abolished. Motility remained inhibited during hypotension maintained for 30–82 minutes at 30–40 mm. During re-infusion of all blood previously removed, tonus returned at 40–50 mm.; peristalsis appeared at 50–75 mm. At the height of the blood pressure rise, tonus and peristalsis often exceeded pre-bleeding levels. Eventually spontaneous, gradual falls in blood pressure occurred, though tonus and peristalsis remained unchanged or even increased until after death. After transfusion, however, marked drops in blood pressure, produced by small blood losses, depressed tonus and peristalsis.

In adrenalectomized dogs minimal or no reduction in tonus or peristalsis occurred when pressure fell spontaneously or by hemorrhage to 30–40 mm. Peristalsis increased, and became abnormal in character, as hypotension continued. Re-injection of blood caused increase of tonus and peristalsis became more normal. As blood pressure fell again the high tonus was retained, and peristalsis became abnormal. Nephrectomized, or intact acutely laparotomized dogs required lower blood pressures to depress motility than intact chronic Biebl loop preparations.

Influence of absorbents on the incidence and induction period of experimental liver tumors. A. H. HANSZEN (by invitation) and W. A. SELLE, *Dept. of Physiology, The Univ. of Texas, Medical School, Galveston.* In a preliminary report it was indicated that montmorillonite, a natural white clay, has a high adsorption capacity for carcinogenic butter yellow (paradimethylaminoazobenzene). It was further shown that the inclusion of this adsorbent in a diet of butter yellow, fed to rats, decreased the onset of fatal liver tumors. During 175 days of the initial test period only 1 of 20 montmorillonite-fed animals developed palpable liver tumors; 17 of 20 control rats developed such tumors and died within a few months.

Further observation of the animals has now inicated that although the induction period of liver tumors was greatly increased by the addition of this absorbent to the carcinogenic diet, the tumor incidence was not altered. All animals receiving the adsorbent eventually developed fatal liver tumors, but only after an induction period which was 50% greater than that of the controls.

The results do not preclude the possibility that with lower dosages of the carcinogen the incidence of such tumors might be lowered by feeding the adsorbent.

Effect of urea peroxide on smooth muscle. JUANITA THACKER HART (by invitation) and W. A. SELLE. *Dept. of Physiology, Univ. of Texas, Medical School, Galveston.* Small amounts of urea peroxide, added to oxygenated Ringer's solution bathing strips of guinea pig intestine, produce marked contractions, the duration and the extent of which vary with the amount added. The response is unaffected by previous treatment with atropine. 0.1 cc of a 1 per cent solution, added to 100 cc of Ringer's produces effects which are somewhat similar to those produced by histamine; the increased tonus, however, is not sustained as in the case of histamine, and the spontaneous contractions are eventually inhibited rather than augmented. As little as 0.05 cc of a 1 per cent solution produces definite responses in the more sensitive segments. With repeated additions of the peroxide the tissue responds less and less. If the Ringer's is changed after each addition, sensitivity is retained for eight or more applications.

While the effects on guinea pig intestine are striking, those on the uterus are only slight; the chemical is entirely ineffective on smooth muscles of arteries and spleen of the dog.

The stimulating effect of urea peroxide on the guinea pig intestine is apparently independent of changes in pH, for solutions neutralized with $NaHCO_3$ or Na_2CO_3 are equally effective, as are slightly alkaline solutions. Nor is the effect due to urea itself, for strong solutions of the latter are not followed by typical responses. On the other hand, an equivalent amount of hydrogen peroxide produces identical responses.

On protection against fatal shock from burns by extracts of liver. H. O. HATERIUS and ELIZABETH GLASSCO (by invitation). *Dept. of Physiology, Wayne Univ. College of Medicine, Detroit, Mich.* Attempts have been made to repeat the observations of Prinzmetal *et al.* (1943), who reported that pretreatment with certain commercial preparations of liver extract served to protect rats

against death from the shock resulting from burns. The procedure consisted essentially in the injection intraperitoneally, one hour before burning, of 1cc./gm. body weight of Lederle extract, representing 15 U.S.P. antianemia units. Burning was produced by immersion, under ether anesthesia, in water at 70°C for 15 seconds. Mortality rates were observed during the ensuing 50-hour period, during which time food and water were withheld.

Over 100 rats, to date, injected with extract have shown a 24.25 per cent mortality. A similar number of control animals, injected with equivalent quantities of saline solution, have averaged 57.25 per cent mortality in the 50-hour period, and uninjected control animals, 66.00 per cent mortality.

The pattern of organization within the primary tactile area of the cerebral cortex of the cat. GEORGE J. HAYNES (by invitation), and CLINTON N. WOOLSEY. *Dept. of Physiology, School of Medicine, The Johns Hopkins Univ., Baltimore, Md.* With the aid of electrical methods for detecting and recording cortical potentials evoked by discrete localized stimulation of tactile receptors in the skin, a detailed study has been made of the pattern of representation in the primary tactile area of the cat's cerebral cortex. The dorsolateral and medial aspects of the hemisphere were explored in millimeter steps and the cutaneous area activating each point was carefully determined.

The results show that the pattern of organization in the cat is fundamentally the same as that previously demonstrated in a similar study on the monkey (Woolsey, Marshall and Bard, *Bull. Johns Hopk. Hosp.*, 1942, **70:** 399–441). Pre- and postaxial surfaces of the hindlimb are represented respectively on the dorsal and medial aspects of the hemisphere, as in the monkey. There is also an "upper head" area, similar to that seen in the monkey, adjacent to the trunk area, and the detailed pattern within the face area of the two animals is similar. In these and in other respects the intra-areal patterns of organization are comparable in cat and monkey. The chief differences to be found are in the relative amounts of cortex devoted to different portions of the body surface.

In accord with the earlier findings on the monkey we may conclude that in the cat, as in the monkey all spinal cord segments below C_8 are projected to the cortex in their spinal sequence and that the cervical segments on projection are reversed *en bloc*.

The effect of high vitamin C and B vitamin intakes on the ability of man to work in hot environments. AUSTIN HENSCHEL (by invitation), HENRY LONGSTREET TAYLOR (by invitation), OLAF MICKELSEN (by invitation), JOSEF M. BROZEK (by invitation) and ANCEL KEYS. *Lab. of Physiological Hygiene, Univ. of Minnesota, Minneapolis.* Fifty-two normal young men were studied for the critical period of the first 2 to 4 days in the heat under rigidly controlled conditions of diet, work and environmental conditions. The temperature was 110–120°F. in daytime and 85–90°F. at night. Relative humidity was 25–30 per cent saturation. The daily vitamin supplementation, which was started 3 days before exposure to heat, was either 200 mgs. of ascorbic acid or 5 mgs. thiamine, 10 mgs. riboflavin and 100 mgs. nicotinamide. The control groups received placebos identical in appearance. Pulse rates during work and recovery, blood pressure during work, rectal temperatures, Crampton blood ptosis tests, rate of sweating, water balance, strength tests, flicker fusion frequency, plasma protein, plasma chlorides and sweat composition were studied. The high vitamin intake had no beneficial effect on the physiological, biochemical or psychomotor functions measured. The rate and degree of acclimatization, the incident of heat exhaustion and the ability to do hard work in the heat were not influenced by the vitamin supplementation contrary to the claims of others. [*This work was supported in part under the terms of a contract (no. OEMcmr-220) between the Reagents of the Univ. of Minnesota and the Office of Scientific Research and Development. Support from other sources will be acknowledged in final publication.*]

The measurement of regional differences in the arterial blood flow in the skin. ALRICK B. HERTZMAN. *Dept. of Physiology, St. Louis Univ. School of Medicine.* My previously reported measurements of regional differences in the arterial blood supply of the skin were based on the amplitudes of the photoelectrically recorded skin pulses. These in turn were expressed in terms of an arbitrary unit, the "filter unit" (Am. J. Physiol. **124:** 328, 1938). Calibration of this unit in terms of blood flow has now been effected by calorimetric measurements of flow in the terminal phalanx of the finger and by measurements of flow in forearm skin by the venous occlusion method. In the former calibration, one "filter unit" was found to be equivalent to a flow of 0.089 cc./sq.cm./min. and, in the latter case, to a flow of 0.115 cc./sq.cm./min. The first value is probably more accurate.

Expression of the previously recorded skin pulses in terms of flow (with the aid of this equivalent of the "filter unit") and making allowances for the surface area of the part yields the following values for the contribution of each region to the average value of the cutaneous blood flow as expressed in cc./sq.m./min: head and neck 51; trunk 93; thighs 51; legs 23; hands 58; feet 27. The sum, 341 cc./sq.m./min., is of the same order as values for cutaneous flow which obtained from calorimetric data or from the rate of helium uptake by the skin. Values, in each type of experiment, are

for partial but not complete thermal dilatation in the skin.

Plasma concentrations following single oral doses of the principal cinchona alkaloids. EDWIN P. HIATT and GERTRUDE P. QUINN (by invitation). *New York Univ. College of Dentistry.* Studies of the plasma concentrations after taking oral doses of quinine, quinidine, cinchonidine, cinchonine and totaquina were made using normal dental students as subjects. The alkaloids were administered in the form of the free base. Plasma samples were taken at once, two, three, five and twenty-four hour intervals after the drug was administered.

With equivalent doses there are marked differences in the plasma concentrations reached after taking different cinchona alkaloids. Quinine gives the highest with peak concentrations, after a dose of 10 mgm. per kilogram of body weight, averaging around 3 mgm. per liter, cinchonidine and quinidine next with around 2 mgm. per liter, while cinchonine gives very low concentrations, not more than 0.5 mgm. per liter.

The plasma concentration after administering totaquina is about what would be expected from the additive effect of the constituents.

The plasma concentration is markedly lower if the dose is administered immediately after a meal.

Tissue concentrations of the four principal cinchona alkaloids in relation to plasma concentration. EDWIN P. HIATT and GERTRUDE P. QUINN (by invitation). *New York Univ. College of Dentistry.* Unanesthetized dogs were perfused intravenously with solutions of the sulfates of quinine, quinidine, cinchonine and cinchonidine in such a manner as to maintain concentrations in the plasma of 3 to 4 mgm. per liter for an hour. Then the dogs were sacrificed and samples of nine tissues taken. These samples were analyzed the same day by an adaptation of the colorimetric method of Brodie, (unpublished), and the tissue/plasma concentration ratio determined.

There is some variation in the degree to which the different alkaloids are concentrated in any one tissue. Cinchonine and quinine correspond closely while cinchonidine and quinidine occur in higher concentrations.

There is a marked difference in the degree of concentration of the alkaloids in different tissues. Skeletal muscle and brain show the lowest, having tissue/plasma ratios of .70 to 5.0. Intestine is next with ratios of 3 to 8. Lung, spleen and pancreas show the highest concentration with ratios of 10 to 27, with liver and kidney usually slightly less. The cerebrospinal fluid in all cases had a much lower concentration of alkaloid than the plasma.

Pyruvic acid balance of the brain. WILLIAMINA ARMSTRONG HIMWICH (by invitation), EDMUND HOMBURGER (by invitation) and HAROLD E. HIMWICH. *Dept. of Physiology and Pharmacology, Albany Medical College, Union Univ., Albany, N. Y.* In studies of brain metabolism 38 observations were made of cerebral pyruvic acid balance of 33 psychotic patients in a variety of physiologic conditions. The blood samples were drawn from the internal jugular vein and the brachial artery. In 36 of these observations the level of pyruvic acid was definitely greater in venous blood from the brain than in arterial blood. The average difference, 0.27 mg. %, though small, is consistent. Of the remaining two observations, arterial and venous concentrations of pyruvic acid were the same in one patient and the arterial level of this metabolite was higher than the venous in the other patient.

For eleven of the patients studied in the post-absorptive state determinations were made of the glucose, lactic acid, pyruvic acid, and oxygen contents of the blood entering and leaving the brain. The average arterial-venous differences were 5.8 volumes per cent, 11 mgm. per cent, 1.7 mg. per cent, and 0.2 mg. per cent, for oxygen, glucose, lactic acid and pyruvic acid respectively. The lactic-pyruvic acid ratio was 7.2.

The oxygen content of blood in the right auricle and right ventricle. J. P. HOLT and P. K. KNOEFEL (by invitation). *Depts. of Physiology and Pharmacology, Univ. of Louisville School of Medicine, Louisville, Ky.* In the determination of cardiac output by the direct Fick principle a number of workers have taken the sample of mixed venous blood from the right auricle. In repeated determinations in the dog by this method we found marked differences in the cardiac output. It was felt that incomplete mixing of blood in the right auricle might explain these differences.

In barbitalized dogs samples were collected simultaneously from two points in the right auricle 25 mm. apart, by means of small steel cannulae that passed into the right auricle by way of the right external jugular vein. The blood was collected over mercury without contact with air and analyzed for oxygen content in duplicate by the method of Van Slyke and Neill. In one experiment the oxygen content was the same in the two samples, while in three experiments it was different, the average difference being 0.91 cc. of oxygen per 100 cc. of blood. Similar experiments were performed by taking samples simultaneously from the right auricle by cannulation, and from the right ventricle by needle puncture. The oxygen content of the blood from these points differed in eight experiments, the average difference being 2.49 cc. per 100 cc. of blood. The oxygen content was the same in two experiments. In two control experiments in which simultaneous samples were withdrawn in a similar manner from well-mixed blood in a bottle, the average difference in oxygen content of the samples was 0.19 cc. per 100 cc. It

appears that in dogs there usually is not complete mixing of blood in the right auricle.

Relative toxicity of commercial benzene and a mixture of benzene, toluene and xylene. VICTOR H. HOUGH (by invitation) and SMITH FREEMAN. *Dept. of Physiology, Northwestern Univ. Medical School, Chicago, Ill.* Studies on the relative toxicity of commercial benzene (90–95 per cent C_6H_6) and a synthetic mixture consisting of 60 per cent benzene, 35 per cent toluene and a 5 per cent xylene have been made over a period of 123 weeks by exposing dogs to an atmosphere containing the solvent fumes. The concentration of solvents was varied from 600 ppm to 1000 ppm by volume and the duration of exposure was varied from 30 to 42 hours per week. Nine dogs were exposed to benzene and 4 dogs to mixed solvent fumes. An adequate diet was fed.

Weekly determinations were made of R.B.C., W.B.C. and Hb., blood phenols and urine conjugated sulfates and phenols. These, plus survival time, were used as criteria of toxicity.

During exposure periods when the concentration of each solvent was equal, the benzene group consistently exhibited higher percentages of conjugated urine sulfates, higher blood and urine phenols, lower white cell counts and lower survival time. When the concentration of benzene was decreased to 600 ppm and the results of the tests were compared to those obtained simultaneously on the mixed solvent group receiving 1000 ppm the values fell within the same range.

No dogs died from exposure to 1000 ppm of the mixed solvent during the 123 week period. Three benzene dogs died during exposure of 1000 ppm (in 4, 10, and 37 weeks), and one died after 42 weeks of exposure to 750 ppm. On the basis of the tests used it is concluded that the toxicity of the solvents as administered was directly related to the amount of C_6H_6 present in the solvent. [*This study was assisted by a grant from the Velsicol Corporation.*]

Factors affecting the anomalous freezing of egg yolk. EVELYN HOWARD. *Dept. of Physiology, Johns Hopkins Univ. School of Medicine.* While Straub and others have reported that egg yolk is hypertonic to white, the author's cryoscopic data (Jour. Gen. Physiol. '32) indicated that the yolk is isotonic to white. However, after seeding supercooled yolk the temperature sometimes tended to plateau at 0.56°, after which it plateaued at −0.43°C. The first plateau was regarded as an anomalous result of supercooling and on theoretical grounds the second plateau was considered the freezing point. The first plateau accounted for the observations of Straub and others.

The freezing of yolk has been further analyzed as follows: stirring and bath temperatures were regulated so that the rate and overall direction of heat transfer (dH) could be adjusted. Since stirring was intermittent, 10 second periods of cooling and ice formation alternated with 20 second periods of warming and ice melting, the overall trend being either +dH or −dH. The −dH yolk seeded at 0.46°C, plateaus at 0.43°C, for 40 minutes or more, if −dH is not excessive. If the +dH yolk is supercooled and seeded the temperature curve inflects at −0.56°, but plateaus at 0.43°. Since the −0.43° plateau occurs on both +dH and −dH if the stirring is adequate it is concluded that it represents the temperature of ice-yolk equilibrium.

The supercooled −dH yolk plateaus at 0.56°. The lower plateau is conceivably a result of substances interferring with equilibrium at the ice-yolk interphase.

These findings support my earlier conclusion that egg yolk is hypotonic to adult blood, and isotonic to egg white.

Influence of immobilization on denervated skeletal muscles. O. LEONARD HUDDLESTON (Medical Corps, A.U.S.) HAROLD DALTON JENKINS (by invitation) JOSEPH TIMOTHY LUCAS (by invitation). *Dept. of Physiology and Pharmacology, Univ. of Colorado School of Medicine, Denver.* Antagonistic skeletal muscles (gastrocnemius-plantaris and anterior tibial) were immobilized in different positions during degeneration and regeneration of their motor nerve supply. Complete degeneration was accomplished by crushing the anterior nerve roots of L 5, L 6, L 7, and S 1. The right hind leg of 8 dogs was casted in extension, 4 in neutral and 3 in flexion. There were two control groups of 6 dogs each (operated uncasted) and (unoperated casted). Determinations were made of muscle weights, tension myograms and electrical tests (thresholds for galvanic and faradic stimulation). Symmetrical muscles of the normal left leg of each animal were used as controls. The average per cent weight loss for the immobilized denervated muscles ranged from 40% to 60%; that of the operated uncasted group ranged from 22% to 28%; and that of the immobilized non-denervated group ranged from 27% to 37%. The total weight loss of the immobilized denervated muscles resulted from two sources of approximately equal value: 1, disuse atrophy; 2, incomplete regeneration. Muscle tension and electrical tests were qualitatively similar to those of the muscle weights. Absence of immobilization of denervated muscles did not retard the regeneration of the motor nerve supply. Recovery was more complete in the non-immobilized denervated muscles. All qualitative and quantitative data indicated that immobilization retarded the reinnervation of denervated muscles. The muscles which were immobilized in the position of maximal muscle length showed less functional recovery than those immobilized in minimal muscle length.

[*Aided by a grant from The National Foundation for Infantile Paralysis, Incorporated.*]

Resistance to the anoxia of high altitude afforded by thiouracil. A. M. HUGHES (introduced by E. B. Astwood). *Depts. of Pharmacology and Medicine, Harvard Medical School, Boston, Mass.* Thyroidectomized animals have been shown to be more resistant to anoxia than normal ones. In view of the fact that functionally athyroid animals can be produced by the administration of thiouracil, experiments were conducted to determine whether rats thus treated would show an increased resistance to anoxia.

Thiouracil was administered to young adult rats as a 0.1% solution in the drinking water. The animals were exposed to a simulated altitude of approximately 38,000 feet (150 mm. Hg.) in a chamber consisting of a vacuum desiccator connected to a water-pump. The pressure was regulated by a valve on the air inlet tube. No difference in survival was noted between the treated and control animals during the first 7 days of treatment. After 8 days treatment with thiouracil, treated animals survived an average of 44 ± 14 minutes, while controls survived for 18 ± 4 minutes. Treatment for 2 to 3 weeks increased the survival time to as long as 8 hours, compared with 10 to 15 minutes for the controls. The injection of 5 μg. thyroxin daily concurrently with thiouracil treatment completely abolished the beneficial effects of the thiouracil.

Protection was also afforded against the anoxia produced by low oxygen tension at atmospheric pressure and by carbon monoxide poisoning. No increase in resistance to cyanide poisoning was observed.

Effect of two adrenal steroids and insulin on the excretion of sodium and chloride. DWIGHT J. INGLE and RUTH SHEPPARD (by invitation). *Research Laboratories, The Upjohn Company, Kalamazoo, Mich.* Normal male rats on a constant diet were used. The administration of 2 to 5 mgm. daily of either 17-hydroxycorticosterone or 17-hydroxy-11-dehydrocorticosterone caused an increased urinary excretion of sodium and chloride for one to three days, followed by a short period of increased retention and thereafter a normal balance between intake and excretion.

When insulin was injected in amounts which produced hypoglycemia there was a similar increase in the excretion of sodium and chloride, a short period of increased retention and then equilibrium. Hypoglycemic convulsions were always followed by a temporary increase in the excretion of these ions.

An increased excretion of sodium and chloride is known to be induced by anoxia, diabetic shock, severe surgery and other unrelated conditions which represent a stress to the animal. It may be possible to extend the suggestions of Lewis et al. (Jour. Clin. Invest., **21**: 33, 1942) and explain this phenomena as due specifically to the increased secretion of the $C_{11, 17}$-oxygenated adrenal steroids during stress. As an alternative hypothesis, it may be that the sodium and chloride excreting effect of these steroids is non-specific, not a physiologic property, and that the phenomena can occur in the absence of these compounds.

Circulation time in normal and in shocked animals, measured by an objective method. (Methylene blue, photo-electric cell.) BENJAMIN JABLONS and OTIS M. COPE. *Dept. of Physiology and Biochemistry, New York Medical College, Flower and Fifth Avenue Hospitals.* The animals used were dogs weighing from 12 to 20 pounds. Materials used consisted of detector apparatus, photo-electric cell, light set-up with galvanometer, and ampoules of methylene blue, 1.2%. The dye was injected into the saphenous vein of the lower extremity or the ulnar vein of the fore limb. The light set-up was adjusted to the ear, and the circulation time, determined by a stop-watch, was taken as the time from the moment of injection of the dye to the instant the galvanometer deflection signalled its appearance in the ear vessels. Shock was produced by ligation of the limbs for varying periods, e.g., ligation of both limbs for 5 to 5½ hours; of all four limbs for 4 hours; or of one limb for 9 hours, prior to release.

Certain precautions are necessary for satisfactory results. To facilitate adequate transmission of light through the ear, all hair should be removed both inside and outside the ear at the place of application of the photoelectric cell, by the use of a depilatory, such a barium sulphide. As little compression as possible should be used to keep the cell in place.

The average circulation time (fore-paw to ear) was, in the normal animal, 7.6 seconds; in the shocked animal, 18.5 seconds. In some animals there was a prolonged circulation time following barbiturate anesthesia in contrast to that following morphine narcosis.

The evaluation of gelatin as a plasma substitute by the use of a standardized method of assay. MARTHA JANOTA (by invitation), S. O. LEVINSON (by invitation), F. ARIMOTO (by invitation) and H. NECHELES. *Samuel Deutsch Serum Center and from the Dept. of Gastro-Intestinal Research of Michael Reese Hospital, Chicago.* Two, 4 and 8% gelatin solutions were assayed on dogs in hemorrhagic shock produced by the method described above. Saline-red cell and plasma-red cell infusions served as controls. The following results were obtained: Saline and 2% gelatin; 15 animals with factors varying between 1940 and 4000 died early; only one animal, with the highest factor yet observed, 4704, survived indefinitely. Four %

and 8% gelatin: 13 dogs with factors below 1700 died early, 4 died during the night. With factors above 1700, 7 died early, 7 during the night, and 11 survived indefinitely.

Whole blood: 5 dogs with factors below 1700 died early, one died during the night, and one survived indefinitely. With factors above 1700, one died during the night and 5 survived indefinitely.

Under the rigid conditions of the assay, 4 and 8% gelatins appear to be good plasma substitutes.

Repeated hemorrhage and later reinfusion of the withdrawn blood is able to produce the typical picture of shock, as evidenced by gross and histologic changes and by changes in the composition of the blood. The development of this shock cannot be prevented by infusions with saline or 2% gelatin solutions. The "Factor Of Probable Survival" (blood pressure times CO_2, 30 minutes after first hemorrhage) gives an expression of biologic variations between animals, and predicts the chances of survival with plasma substitutes.

Vascular reactions to cold related to the early stages of immersion foot. KENNETH E. JOCHIM and ALRICK B. HERTZMAN. *Dept. of Physiology, St. Louis Univ. School of Medicine, St. Louis, Mo.* The vascular reactions in the finger pad of normal subjects to ice water were studied by recording simultaneously the amplitude and wave form of the pad pulses and the changes in blood content by means of photoelectric plethysmographs. The reactions could be divided into two groups: first, those in which the changes in blood content closely paralleled the changes in arterial diameter without any significant effect on the propagation of the pulse wave into the minute arteries; second, those in which the onset of the reactive dilatation showed first in a large early increase in pad blood content which preceded and then paralleled the increase in the pad pulses. This engorgement of the pad increased its volume often far above the control levels; the skin capillaries flushed suddenly at this time; the hyperemia was evident on inspection. The pad pulses of this second group also exhibited gross changes in wave form (slow ascent of anacrotic limb, delay of crest, marked rounding) as the increase in blood content proceeded but progressively recovered their normal form as the peak of the increase in blood content was passed.

These differences between the two groups may be related to quantitative differences in the participation of the arterio-venous anastomoses and normal arteriolar channels in the early stages of the reactive dilatation. It is felt that the reactions of the second group would favor the development of the "immersion foot" syndrome due to the engorgement of the subpapillary venous plexus and capillary stasis. [*Aided by American Medical Association.*]

The effects of cold on the blood vessels of the skin of the forearm. KENNETH E. JOCHIM and ALRICK B. HERTZMAN. *Dept. of Physiology, St. Louis Univ. School of Medicine, St. Louis, Mo.* Differences between the skin of the forearm and of the finger with respect to the richness of the arterial blood supply and the number of arterio-venous anastomoses correlate with significant differences in the vascular reactions (recorded by photoelectric plethysmographs) to local cold. Decreases in the blood content and the volume pulses of the forearm skin were elicited in proportion to the duration and the extent of the fall in skin temperature. However, the volume change preceded the decrease in pulse amplitude, and, in the case of a brief application of cold, often occurred without a change in pulse amplitude. Blocking the blood supply to the hand by a cuff at the wrist did not alter these reactions. Recovery in skin temperature, skin pulses, and skin volume was very slow compared to recovery in the finger. No reactive dilatation was seen in the forearm skin.

It is believed that the direct effects of cold on the skin vessels are dominant (vasomotor reflexes being of minor importance) and that the volume changes in the forearm skin are due principally to changes in tone of the subpapillary venous plexus which seems to be quite sensitive to cold, and that the nonappearance of the reactive dilatation which accounts for the corresponding slow recovery and the absence of venous engorgement (the latter occurs frequently in the finger), is due to the dearth of arterio-venous anastomoses. Their distribution therefore seems relevant to the topography of the skin lesions in the "immersion foot" syndrome. [*Aided by Americal Medical Association.*]

Damaging effect of lipemic plasma upon erythrocytes in normal man and in pernicious anemia. VICTOR JOHNSON, L. WILLARD FREEMAN (by invitation) and JOAN LONGINI (by invitation) and ARTHUR LOEWY (by invitation). *Dept. of Physiology, the Univ. of Chicago.* The authors and other collaborators have previously reported that in dogs (1) especially lacteal chyle but also thoracic duct chyle are hemolytic during fat absorption; (2) the hemolytic agents are probably fatty acids and soaps; (3) lipemic plasma increases erythrocyte fragility; and (4) a high fat diet increases the rate of erythrocyte destruction.

Employing a standard erythrocyte fragility test it was found (111 experiments) that exposure to normal lipemic serum increased the susceptibility of normal erythrocytes to hypotonic hemolysis. Upon exposure to normal lipemic serum, the erythrocytes of 2 untreated pernicious anemia patients were rendered more fragile than were the erythrocytes of normal individuals, 5 treated per-

icious anemia cases, and 7 patients with other nemias.

In 8 untreated pernicious anemia patients ipemic serum produced not only an increased rythrocyte fragility but also actual hemolysis, hen lipemic serum and red cells of the same individual were mixed. By contrast, lipemic serum f 6 treated pernicious anemia patients and 7 ormal individuals produced only increased agility but no actual hemolysis of their own red lood cells.

This evidence supports the concepts that fat ngestion contributes to normal daily human rythrocyte destruction, and is especially inurious to the erythrocytes in untreated pernicious nemia.

A note pertaining to Cushing's conclusion that "total hypophysectomy" was incompatible to life. A. D. KELLER. *Dept. of Physiology and Pharmacology, Baylor Univ. College of Medicine.* It is clear hat death in Cushing's "totally hypophysectonised dogs" was predominately due to spontaneous hypoglycemic crises (cachexia hypophysepriva). Why did crises invariably precipitate in Cushing's animals and not for instance in those of Aschner, Sweet and Allen and Dandy and Reichert?

I suspect that the consistency of Cushing's results was due to his consistency in severing the stalk as far distally as was compatible with total removal of the pars anterior.

This suspicion is based upon my experience in executing varying degrees of hypophysectomy in a large series of dogs wherein the postoperative nursing and feeding care for the entire series was carefully standardized. They were maintained in a constant environmental temperature, fed at 8 hour intervals (force fed when necessary) and observed routinely at 4 hour intervals.

Dogs passed through the acute and subchronic periods with relative ease when the stalk was cut; (1) distally such that a narrow rim of pars anterior remained attached or (2) through its middle or proximal extent, preliminary to the hypophysectomy. When it was sectioned as close as possible to the pars anterior, without cutting into this structure, it was extremely difficult to maintain these preparations during these periods.

This increased maintenance difficulty and its correlation with the level of stalk section was unmistakable. Hypoglycemic crises precipitated with ease and were extremely difficult to control by sugar therapy. Therefore, factors other than carbohydrate disturbances are suspected as contributing to the extreme instability of these particular preparations. [*Aided by a grant from the Rockefeller Foundation to the Univ. of Alabama.*]

An intense and enduring miosis following transection of the brain stem caudal to the level of exit of the oculomotor nerves. A. D. KELLER. *Dept. of Physiology and Pharmacology, Baylor Univ. College of Medicine.* In my original paper describing a method of transecting the brainstem without disturbing the brain tissue cephalad to the lesion it was stated that the pupils assumed a state of maximal constriction when the transection passed caudal to the level of exit of the oculomotor nerves. This statement pertained to observations on acute and subacute preparations only. Bremer has independently noted this miosis in similar preparations.

Since the original observation, aside from establishing its invariable occurrence in a very sizable number of cats and dogs as well as a few monkeys, I have been much interested in determining the status of the pupils in truly chronic preparations. I have succeeded in maintaining several such preparations for from six to eight weeks. Following an uncomplicated complete transection there is no evidence of a lessening of the miosis for the first few weeks after operation. Then very slowly but progressively the pupils exhibit slight dilatation when observed in total darkness or in mild light. As soon as the pupils dilate sufficiently to admit light to the retina a light reflex can be demonstrated. An intact pupillary response to light can be demonstrated shortly after operation in the situation where the lesion encroaches upon the pupillo-constrictor cells or fibers such that the pupil remains sufficiently dilated to admit light to the retina.

Following near-complete transections, a small area remaining unsevered either medially or laterally, the pupils exhibit maximal constriction for several days but then return to normal rapidly, i.e. with respect to somatic pupillo-dilator influx. Indeed the status of the pupils is a most reliable physiological criteria for judging the completeness of transection, during the subchronic and chronic periods. [*Aided by grants from the Rockefeller and John and Mary R. Markle Foundations to the Univ. of Alabama.*]

Death in from three to six weeks following uncomplicated total hypophysectomy apparently due predominantly to adrenal insufficiency. A. D. KELLER. *Dept. of Physiology and Pharmacology, Baylor Univ. College of Medicine.* In the dog it has been found that complete sexual regression and stoppage of growth with maximal coat change can routinely be precipitated unassociated with material disturbances in carbohydrate and energy metabolism or adrenal cortex size. The appropriate hypophysectomy is that which leaves the maximal amount of stalk tissue compatible with total or near-total elimination of the pars anterior.

Quantitatively the disturbance in carbohydrate, energy and fat metabolism and adrenal atrophy is associated with the level of stalk section pre-

liminary to the hypophysectomy. The more proximal the section the greater are these deficits.

When all hypophysial tissue (including stalk tissue) is removed without infringement upon the hypothalamus the animals make uneventful recoveries and appear normal outwardly for from three to six weeks (more often at four weeks). Then a characteristic crisis sets in abruptly. Diarrhoea first appears followed by muscular weakness and general lassitude. Mild hypoglycemia is present and, according to not too reliable determinations, blood sodium is abruptly lowered. Keeping blood sugar at or above normal does not alter the course of the crisis. Crises have been successfully alleviated by administration of Upjohn's Adrenal Cortex Extract and Ciba's Percortin. Successful therapeutic management is not as predictable as following adrenalectomy alone, due presumably to associated multi-glandular deficits.

Adrenals in dogs dying in four weeks exhibit striking but not maximal thinning, while in dogs maintained therapeutically three months the adrenals are maximally atrophied. Adrenals of near-total hypophysectomized dogs maintained three months invariably exhibit profound atrophy. Crises can be precipitated in near-total preparations by lowering diet sodium. [*Aided by a grant from the Rockefeller Foundation to the Univ. of Alabama.*]

Demonstrating that descending fibers subserving heat production are distributed well latero-ventrally at the cephalic level of the pons. A. D. KELLER. *Dept. of Physiology and Pharmacology, Baylor Univ. College of Medicine.* A transverse lesion placed in the cephalic pons such that in addition to a right hemisection approximately the medial two-thirds of the left half is severed temporarily impairs heat regulation. The animal's ability to maintain a normal rectal temperature in the presence of a cool environment is totally eliminated for several days. Then gradually over a period of three weeks this ability returns essentially to normal.

After recovery has occurred severing the intact lateral segment by making a left hemisection a few mm. cephalad to the original lesion, reduces the animal *permanently* (8 weeks) to the totally non-heat regulatory state. Accordingly the recovery is interpreted as being due to the activity of fibers, subserving heat production, descending in the unsevered lateral segment rather than to the progressive activity of a released subsidiary pontile or medullary mechanism.

These fibers pass in the ventral portion of such an isolated lateral segment because when this portion is included in the original transverse lesion, (complete transection except for the dorso-lateral tissue in immediate environs of the left brachium conjunctivum) the animal loses *permanently* all powers to combat a cool environment. Such a preparation retains adequate heat loss powers to combat a hot environment without noticeable or a striking deficit. Such a lesion therefore completely eliminates the heat production mechanism without materially impairing the heat loss mechanism. [*Aided by a grant from the John and Mary R. Markle Foundation to the Univ. of Alabama.*]

Failure of the cerebrospinal tract to exhibit retrograde degeneration following section at the pons or midbrain level. A. D. KELLER. *Dept. of Physiology and Pharmacology, Baylor Univ. College of Medicine.* The statement is frequently made that section of all nerve fiber systems within the central nervous system results in the retrograde degeneration of the fibers and cell bodies proximal to the lesion. During the past several years I've had repeated occasions to observe that this does not obtain with respect to the cerebrospinal tract when it is severed at the pons or midbrain level using the *blunt dissection method.*

Dogs (also cats and monkeys for shorter intervals) were maintained for from 6 to 15 months following a complete hemisection of the upper brainstem. After termination of the experiment the brainstems were fixed in formalin, embedded in paraffin, sectioned serially (crossed and frontally) and then appropriate sections were stained in several ways; modified Pal Weigert, modified Maximow, cresyl violet and Bodian silver.

Study of the cerebrospinal tracts above the level of hemisection revealed no obvious difference between the severed and unsevered tracts. Below the level of hemisection the severed tract showed complete degeneration.

The above facts were illustrated incidentally before this society in 1939 in connection with a motion picture demonstration pertaining to muscular atonicity following transection of the brainstem through the cephalic pons. (Am. J. Physiology **126**: 552, 1939.)

It has previously been demonstrated that fibers in a brachium conjunctivum likewise do not show retrograde degeneration, whereas those in the rubro-spinal tracts do (complete in two months). Other systems which invariably exhibit retrograde degeneration are fibers taking origin from the substantia nigra and the superior olive. [*Aided by a grant from the Rockefeller Foundation to the Univ. of Alabama.*]

Sensory disturbances in animals having incomplete transections of the brain stem. A. D. KELLER. *Dept. of Physiology and Pharmacology, Baylor Univ. College of Medicine.* Hemisection of the brainstem through the pons or midbrain does not obviously alter sensory perception as judged by

"gross clinical inspection." When in addition to a hemisection the medial aspect of the opposite half is encroached upon appropriately the animal exhibits a clear cut bilateral hypersensitivity to cutaneous stimuli. The response suggests an excruciating painful sensation ("over-reaction"). The threshold is lowered or at least is not raised. This hypersensitivity is particularly noticeable during the early postoperative period and in some preparations disappears with chronicity while in others it persists in demonstrable form indefinitely. I have seen no evidence of spontaneous attacks.

When the opposite half of the brainstem is involved to a greater degree there is a definitely raised threshold but the "over-reaction" painful response is still present. Also a rage response is obtainable which could well be an "over-reaction" affair. Although one can not always predict which response will obtain following a given stimulation it is at times possible, in long chronic preparations, to selectively elicit either response by appropriate stimulation.

There is no doubt of the similarity of the experimental syndrome with the clinical syndrome described by Kendall (Brain, 1939, **62**: 253). There is this difference, Kendall attributes the phenomenon to involvement of one side of the brainstem alone, whereas experimentally it is clear that the involvement *must be bilateral*.

Are the "over-reaction" responses due to selective elimination of specific fibers or merely due to a progressive reduction in number of fibers? [*Aided by a grant from the Rockefeller Foundation to the Univ. of Alabama.*]

Hard work on restricted B vitamins. ANCEL KEYS, AUSTIN F. HENSCHEL (by invitation), HENRY LONGSTREET TAYLOR (by invitation, OLAF MICKELSEN (by invitation) and JOSEF M. BROZEK (by invitation). *Lab. of Physiological Hygiene, Univ. of Minnesota, Minneapolis.* Eight normal young men maintained a rigid 25-day schedule of hard work (4800 Cal. daily) on a diet adequate except for vitamins of the B complex which averaged, per 1000 Cal., 0.16 mg. thiamine, 0.15 mg. riboflavin and 1.8 mg. of niacin. All foods as eaten were analyzed for the several vitamins by proven methods. All men received adequate B supplements for the first 6 and the last 5 days but during the remainder only 3 men received the supplements, while the other 5 received placebos. None knew what he received and all were constantly under supervision. Initial vitamin stores in the body were standardized by a fixed preparatory regime below National Research Council recommendations. Repeated extensive measurements under constant conditions covered hard aerobic (endurance) work, violent (anerobic) exertion, psychomotor functions (speed, coordination) muscle strength, various "fitness" tests and details of intermediary metabolism (blood lactate, pyruvate, glucose) in rest, work and recovery. Exhaustive clinical examinations were supplemented with subjective questionnaires. All results were in conclusive agreement that the vitamin limitation was entirely without effect on all of the functions measured. Urinary excretion of thiamine and riboflavin was frequently measured and this reflected the intake but this was more pronounced with thiamine than with riboflavin. It is concluded that for at least 14 days of very hard work the present low intake of B vitamins has no effect on the physical "fitness," performance or work capacity of normal young men. [*This work was supported in part under the terms of a contract no. (OEMcmr-27) between the Reagents of the Univ. of Minnesota and the Office of Scientific Research and Development. Support from other sources will be acknowledged in final publication.*]

Porphyrins and the central nervous system. HEINRICH KLÜVER. *Otho S. A. Sprague Memorial Inst., Univ. of Chicago, Chicago, Illinois.* The fluorescence spectrum of the white matter of the central nervous system, in various mammals, reveals a sharp emission band at 630-620 mμ with a maximum at about 625 mμ. This band is present even in the white matter of a live animal. It is absent in the cortex and in the meninges of the brain and spinal cord. Exciting light of $\lambda < 470$ mμ is effective in producing this band.

The position of the band and the effects of various agents on the behavior of this band suggest the presence of a porphyrin. Available data strongly indicate that the porphyrin which we have extracted from the white matter of various mammals, including man, has the characteristics of a coproporphyrin. The spectrochemical evidence is derived from data on solubility, specific HCl number, and the fluorescence spectra in different solvents. Extractions of white matter also furnish varying amounts of protoporphyrin.

The 625 mμ emission band has been found to be absent in the white matter of amphibians and reptiles (7 species). It has been found to be present only in warm-blooded animals (20 species of mammals and birds). Postnatal development in mammals appears to be characterized by an "ascending porphyrinization" of the central nervous system. The 625 mμ emission band is not present at birth. It appears first in the spinal cord (e.g., in rats at the age of 20–23 days) and, finally, in the cerebrum.

The fluorescence spectra of the cranial nerves exhibit striking differences in the sense that the 625 mμ emission band is present, for instance, in the 2nd and 8th nerve, but absent in the 3rd and 6th nerve.

The significance of these findings for neurology

and psychiatry and problems related to the presence of a photodynamic substance in the white matter, including the optic nerve, have been discussed in a previous paper (J. Psychol. 17: 209, 1944).

The reabsorption of sulfanilamide by the kidney tubule. GEORGE KOEPF, ROGER S. HUBBARD and TED A. LOOMIS (by invitation). *Univ. of Buffalo Medical School and the Metabolic Clinic of the Buffalo General Hospital.* In a series of 90 renal clearance determinations on an unselected group of human subjects, it was found that the clearance of sulfanilamide was 0.45 times as great as the simultaneous clearance of inulin. This indicated that part of the sulfanilamide which appeared in the glomerular filtrate was reabsorbed through the kidney tubules into the peritubular capillaries.

The sulfanilamide clearances were determined simultaneously with inulin and diodrast. The rate of reabsorption of sulfanilamide could therefore be calculated by subtracting its rate of excretion in the urine (urine sulfanilamide concentration times rate of urine formation) from its rate of excretion in the glomerular filtrate (plasma sulfanilamide concentration times inulin clearance). The rate of reabsorption of this compound was plotted against (1) the plasma flow to the kidneys as given by the diodrast clearance, (2) the rate of urine formation, and (3) its rate of excretion in the glomerular filtrate.

There was no relationship between urine flow and the reabsorption of sulfanilamide. Slight, irregular parallelism between the reabsorption and renal blood flow (measured by the diodrast clearance) was probably present. The correlation between the reabsorption and rate of excretion of the compound into the glomerular filtrate was very close. As the rate of excretion of sulfanilamide into the glomerular filtrate rose from 0.1 to 14.0 mg. per minute the rate of reabsorption rose from 0.1 to 9.0 mg. per minute. By far the most important factor affecting the reaborption of sulfanilamide appears to be the rate at which the compound is delivered to the tubules.

An effect of breathing high oxygen mixtures on shivering in man. FREDERIC J. KOTTKE (by invitation), J. STEPHEN PHALEN (by invitation) and M. B. VISSCHER. *Dept. of Physiology, Univ. of Minnesota.* In the course of studies of the physiological responses to cold, an effect on the gross shivering movements of breathing high concentrations of oxygen was noted.

Subjects nude or dressed in standard garments were seated on a net covered deck chair in a room maintained at 10°C and 45% relative humidity. Thermocouples were used to record skin and rectal temperatures. A radiation pyrometer was used to measure the surface temperature of exposed areas of skin and of the external surface of the garments. The onset and amplitude of shivering were recorded optically using sensitive glass spoon manometers to measure pressure changes in balloons taped over the pectoral muscles and the adductor muscles of the thighs. Oxygen mixtures were supplied through a standard closed circuit metabolism machine.

Under standardized conditions the time of onset of shivering was reasonably constant for a given subject. However, when a high oxygen concentration was breathed by the subject from the beginning of the experiment the onset of gross shivering was greatly delayed. Likewise if the oxygen was administered after shivering movements had become continuous, after about five minutes gross shivering was reduced or completely inhibited for variable periods of time. This was accompanied by a subjective sensation of warmth although skin temperature changes were small or non-existent. On the other hand if the subject was switched from a high oxygen concentration to air the shivering movements quickly increased in amplitude and intensity. [*Aided by grants from the Munsingwear Fund of the Minnesota Medical Foundation.*]

Effect of breathing high oxygen mixtures on human metabolism during shivering. FREDERIC J. KOTTKE (by invitation), J. STEPHEN PHALEN (by invitation) and M. B. VISSCHER. *Dept. of Physiology, Univ. of Minnesota.* The effect of high concentrations of oxygen on the metabolism during shivering has been studied.

In addition to recording shivering of normal subjects as described in the preceding note, the changes in metabolism were estimated using standard apparatus. A resting metabolic rate was determined after thirty minutes rest in a warm room before the subject entered the cold room. In the cold room the subject was seated on a deck chair and remained quiet during the course of the experiment. After the subject had begun to shiver the metabolism mask was applied and the oxygen consumption recorded.

With the onset of shivering the metabolic rate increased markedly. However, although shivering movements were inhibited by oxygen as previously noted the metabolic rate was not decreased. For example from a resting metabolism of 35 Cal/m²/hr. the metabolism rose 26% with the onset of shivering. Then although under the influence of high oxygen mixtures the shivering movements gradually decreased and finally disappeared completely for six minutes the metabolism increased another 14%. As shivering reappeared in spite of the high oxygen concentration the metabolism was further increased 17%.

It appears likely that a high oxygen concentration under the described conditions changes the muscle activity pattern from a clonic to a tonic

type. It is also evident that detectable shivering is not essential to the metabolic rate increase in response to cold. [*Aided by grants from the Munsingwear Fund of the Minnesota Medical Foundation.*]

Comparison of indirect and direct measurements of arterial pressure in dogs. E. H. LAMBERT (by invitation) and G. E. WAKERLIN. *Dept. of Physiology, Univ. of Illinois, College of Medicine.* Blood pressure readings by four indirect "cuff" methods utilizing the fore or hind leg and auscultatory or palpatory criteria were compared with determinations by femoral artery puncture in unanesthetized, trained dogs. Variations of the indirect methods, including the use of different cuff sizes, were tried.

The reliability of the indirect methods at different pressure levels was tested in four dogs with sectioned buffer nerves. In these dogs the blood pressure shows wide fluctuations in a short period of time. More than 600 simultaneous comparisons of indirect and direct pressure readings were made over a range of 130 to 325 mm. Hg systolic pressure. It was not possible with reasonable care to obtain consistently accurate determinations by the indirect methods. Different methods using the hind leg gave readings in some dogs as much as 50 mm. Hg above or below the femoral systolic pressure. In some instances an indirect method gave fair correspondence to direct readings at one pressure level, but not at others. Each dog and each indirect method presented an individual problem.

In fifteen dogs (seven of which were rendered renal hypertensive while under study) blood pressure was measured 2 to 3 times a week for periods up to 18 months by one or more indirect methods and by arterial puncture. Although there was a fairly close parallelism between indirect and direct determinations in some animals, striking deviations occurred. Occasionally bizarre unaccountable changes extending over periods of weeks were obtained in indirect readings, although no change or even an opposite change in direct readings occurred.

Failure to produce arterial hypertension by intracisternal injection of kaolin. E. H. LAMBERT (by invitation) and G. E. WAKERLIN. *Dept. of Physiology, Univ. of Illinois, College of Medicine.* We were unable to produce a significant elevation of arterial blood pressure by the intracisternal injection of kaolin in rats, rabbits and dogs, although the type, amount, mode of preparation and technique of injection of the kaolin were varied. The other effects observed, including changes in pulse rate, increased intracranial pressure and internal hydrocephalus have duplicated those described by previous investigators. The spinal cord has not been described previously. We observed in rabbits and dogs, 23 to 750 days after kaolin injection, marked cavitation of the gray matter of the cervical spinal cord with adhesive arachnoiditis. Previous injection of kaolin and cavitation of the spinal cord did not prevent dogs from developing sustained hypertension following renal artery constriction, or marked temporary elevations of blood pressure following buffer nerve section.

In the dog we have used puncture of the femoral artery to measure blood pressure, whereas previous investigators have, without exception, used indirect cuff methods. An extensive study of the characteristics of the indirect methods in the dog has shown that the production of so-called kaolin hypertension by others probably depended on the use of these methods, which we frequently found to be unreliable.

Foa et al. (Proc. Soc. Exper. Biol. and Med. **46:** 696, 1941) and Page (personal communication) likewise failed simultaneously with us to produce kaolin hypertension in dogs, using arterial puncture to measure the blood pressure. Most probably kaolin hypertension as a significant, persistent elevation of arterial blood pressure does not exist or is extremely rare.

Observations on the blood pressure of dogs following buffer nerve section. E. H. LAMBERT (by invitation) and G. E. WAKERLIN. *Dept. of Physiology, Univ. of Illinois, College of Medicine.* Four dogs were observed for 250 to 490 days after section of the carotid sinus and aortic nerves. Mean blood pressure was measured by femoral artery puncture in a quiet room. For two to three weeks after denervation there was an unstable elevation of blood pressure up to 210 mm. Hg. Thereafter, the blood pressure reached a range (120 to 150 mm. Hg) equal to or slightly above the preoperative level. However, the blood pressure remained markedly unstable, increasing as much as 150 mm. Hg in a few seconds with minor disturbances which caused apprehension or attention without actual struggling. Frequently, the pressure remained high during the first arterial puncture (3 to 5 minutes), but fell during the second or third puncture. The pressure tended to remain high as a result of noise, a strange observer, or infrequent handling, especially in high-spirited dogs.

Because of the marked influence of slight disturbances on these dogs, we studied the effect of measuring the blood pressure in the animal quarters. In this noisy environment the readings were 30 to 100 mm. Hg above values obtained in the quiet room. A fifth dog was observed by another investigator to be hypertensive (220 mm. Hg) three months after denervation when measurements were made in the animal quarters. For one month thereafter we found that in a quiet room, although the initial pressures were 210 to

280 mm. Hg, the final pressures of the first to third arterial puncture were 110 to 155 mm. Hg.

We believe that the difference of opinion as to the occurrence of a permanent hypertension in dogs after buffer nerve section can be explained by differences in the techniques of measuring blood pressure and/or in the conditions under which it is measured.

The effect of temperature change on blood flow through the small intestine. HAMPDEN LAWSON. *Dept. of Physiology, Univ. of Louisville School of Medicine, Louisville, Ky.* Loops of ileum, 10–12 cm. long, were prepared with long mesenteric pedicles in barbitalized dogs, for immersion in a small temperature-controlled bath containing 0.9% NaCl solution. The volume flow of blood into the loop was measured by differential arterial manometry. Control observations were made with bath temperature at 37–38°C.

The immediate effects of temperature change were the reverse of those usually reported for other organs. An increase in flow, as much as 100% above the control rate, was obtained when bath temperature was reduced 10°, while 25–40% decreases were observed when temperature was raised 4°. These effects reached a maximum within 5–10 minutes and slowly subsided, flow through the chilled loop finally reaching a level below, and through the warmed loop above the control rate. The total duration of the anomalous response was 10 to 20 minutes. These responses were obtained with temperature changes as small as 1°, at rates of change as low as 2°/min. The responses were unaffected by section of the mesenteric nerves, and cocainization of the loops. They were obtained equally well on application of heat or cold to the mucosa alone.

Immediate increases in flow were obtained at temperatures above 42°, which persisted for 30 minutes or longer after return to control temperature. During this period anomalous responses were not obtained.

Spreading depression of electrical activity in the cerebral cortex. A. A. P. LEÃO (introduced by Hallowell Davis). *Harvard Medical School, Boston, Mass.* Electrical or mechanical stimulation of the rabbit's cerebral cortex (dial), below threshold for electrical after discharge, markedly depresses the spontaneous electrical activity. The depression successively affects adjacent areas and within 3 to 5 minutes involves all of the dorso-lateral cortex except area Rsgβ of Rose. Recovery of the initial pattern of spontaneous activity requires 5 to 10 minutes at each region. With weak stimulation depression at any region runs the same course regardless of the region stimulated. The wave of depression is most easily initiated in the frontal regions. Only with supraminimal stimulation does the depression spread to the opposite hemisphere, then appearing first in the region symmetrical to the point of stimulation and thence spreading as in the stimulated hemisphere. During depression the cortical electrical responses to touch, illumination of the retina, electrical stimulation of sensory nerves or of the same or the opposite hemisphere, and local applications of strychnine or of eserine plus acetylcholine are all reduced. Shocks applied to a depressed region fail to elicit typical responses in the opposite non-depressed hemisphere. During depression of the spontaneous electrical activity, specific, large, slow, localized waves often appear. One electrode becomes usually negative with respect to others 1 to 3 mm. distant. Fast components may also appear, and the activity when intense closely resembles the "seizure pattern" of experimental epilepsy. A wave of marked arterial dilatation and increased blood flow in the pial veins travels over the hemisphere simultaneously with the wave of depression of electrical activity.

The successful treatment of so-called "irreversible" shock by whole blood supplemented with sodium bicarbonate and glucose. R. LEVINE, B. HUDDLESTUN (by invitation), H. PERSKY (by invitation) and S. SOSKIN. A series of 64 unanesthetized dogs was brought to the "irreversible" stage of shock by repeated bleeding, which was done in amounts and at intervals such as to reproduce a more or less standard pattern for all. This pattern was the rapid reduction of the blood pressure to 50 mms. Hg. or less, and a slower decline over 1½ to 2 hours to the lowest pressures compatible with life. Therapy was withheld until the plasma CO_2 capacity fell to 15 vols. per cent or less.

RESULTS:

No. of dogs	Lowest B.P.* (mm. Hg)	Lowest CO_2 capacity (vols. %)	Therapy†	Dose of supplement (gm./kg.)	Survival (per cent)
8	28	18.6	None	—	0.0
8	27	14.9	W.B.	—	25.0
8	29	13.0	W.B. + Glucose	0.38	37.5
8	29	15.9	W.B. + $NaHCO_3$	0.43	50.0
8	31	13.5	W.B. + NaSucc.	0.42	50.0
8	29	11.7	W.B. + NaLact.	0.58	75.0
16	24	15.8	W.B. + $NaHCO_3$ + Glucose	as above	62.5

* Average for group.
† W.B. = whole blood.

CONCLUSIONS: 1. Acidosis, while not the cause of shock, is an important factor in determining the reversibility of far-advanced shock.

2. A large proportion of dogs ordinarily considered to be in "irreversible" shock will survive if treated with whole blood supplemented by $NaHCO_3$ and glucose. [*The work described in this paper was done under a contract recommended by*

the Committee on Medical Research, between the Office of Scientific Research and Development and the Michael Reese Hospital, Chicago, Illinois (Responsible Investigator, Samuel Soskin).]

A new standardized method to produce shock and assay plasma substitutes. S. O. LEVINSON (by invitation), MARTHA JANOTA (by invitation), F. ARIMOTO (by invitation) and H. NECHELES. *The Samuel Deutsch Serum Center and The Dept. of Gastro-Intestinal Research of Michael Reese Hospital, Chicago.* A uniform method for the evaluation and comparison of blood substitutes is needed badly. The following technic is proposed to overcome this need. Unanesthetized dogs are bled 23, 21, 19, 17 and 15% of their determined blood volumes at hourly intervals. At the half-hour interval following each hemorrhage a volume of plasma substitute equal to the volume of plasma removed is infused, followed by the animal's packed red cells. Ten % additional bleeding is withheld for determinations. The reinfusion of the red cells forestalls development of anemic anoxia.

Blood pressure is recorded. CO_2 content is determined ½ hour after each hemorrhage and each infusion. Resistance to hemorrhage, clinical condition and probable survival is found to be expressed by a value obtained by multiplying the systolic blood pressure by the CO_2 content measured ½ hour after the first hemorrhage, before reinfusion. We have called this "The Factor of Probable Survival." The efficacy of a blood substitute can be determined in animals with a factor between 1700–2000, which we have found to be a critical range. The above method has been employed in over 80 dogs and by applying the "Factor of Probable Survival" we can group the animals according to their biologic variations, thus permitting for a comparison of different plasma substitutes. The return of the red cells eliminates the factor of oligo-erythremic anoxia and provides a more strict method for the assay of substances designed to replace plasma rather than whole blood.

The effect of bile salts on fatty liver production in dogs. TSAN-WEN LI (by invitation) and SMITH FREEMAN. *Dept. of Physiology, Northwestern Univ. Medical School, Chicago, Ill.* Protein-deficient high-fat diets with or without a cholesterol supplement cause fatty livers in dogs, but the degree of infiltration varies greatly. This may be due to poor fat absorption caused by an inadequate flow of bile into the intestine.

23 dogs were included in the present study, 10 were fed a protein-deficient high-fat (33 per cent) diet and 13 were fed the same diet plus cholesterol (0.1 gm./lb. body weight). 3 dogs from each group received 2.8 gm. desiccated ox-bile salts (Wilson) daily with their food.

The decrease in dye clearance and elevation of serum phosphatase were not much influenced by the added bile salts, nor was the degree of lipemia.

All animals were sacrificed when moribund. The fat content of the fresh wet livers were as follows (average figures in parenthesis):

	No. of animals	Total fat (%)	Cholesterol (%)
Without cholesterol:			
No bile salt	7	6.6–31.9 (16.2)	0.23–0.38 (0.27)
With bile salt	3	14.5, 17.9, 24.8 (19.1)	0.44, 0.39, 0.38 (0.40)
With cholesterol:			
No bile salt	10	1.6–43.0 (26.3)	0.59, 3.50 (1.80)
With bile salt	3	28.9, 29.3, 35.4 (31.2)	2.41, 1.35, 1.52 (1.76)

These data suggest that the percentage of fat in the liver is more uniformly high in those animals fed bile salts. A lack of bile salt formation may explain the small amount of fatty infiltration observed in some animals fed a protein-deficient high-fat diet.

The effect of chronic hyperbilirubinemia upon the dye clearance and serum phosphatase of normal dogs. TSAN-WEN LI (by invitation), F. E. SNAPP (by invitation), V. H. HOUGH (by invitation) and A. C. IVY. *Dept. of Physiology, Northwestern Univ. Medical School, Chicago, Ill.* A plasma bilirubin concentration of 14–18 mg. per cent was obtained in 6 dogs by 5 intravenous injections each consisting of 50 mg. bilirubin (Searle) in 50 cc. of dog plasma in 4–6 hours. The decline of bilirubinemia was rapid the first day, less so the second and third days, and its disappearance from the circulation was still incomplete 10–12 days after injection. Rose Bengal clearance decreased to 27–65 per cent (ave. 43 per cent) of normal by the morning following the injection, at which time the plasma bilirubin was 9.3–5.8 mg. per cent (ave. 7.3 mg. per cent). All animals, except one, regained the normal rate of dye clearance by the 8th day. The serum phosphatase remained unchanged throughout the experiment.

A chronic hyperbilirubinemia (ave. about 6 mg. per cent) was maintained in 3 dogs for 4 weeks by repeated injections. The dye clearance decreased to an average of 55 per cent of normal. In a few instances, a slight elevation of serum phosphatase (7–8 Bodansky units) occurred but did not persist.

The injection of similar volumes of plasma alone produced only a very slight depression in dye clearance and slight elevation of serum phosphatase.

The animals with hyperbilirubinemia remained in good health and nutrition.

The experiments indicate that hyperbilirubinemia reduces the dye clearance by liver. The lack of

any correlation between the reduced excretory capacity of the liver and the serum phosphatase is further evidence favoring the view that serum phosphatase is not excreted by the liver.

The effect of dietary protein on the susceptibility of dogs to benzene poisoning. TSAN-WEN LI (by invitation), V. H. HOUGH (by invitation) and SMITH FREEMAN. *Dept. of Physiology, Northwestern Univ. Medical School, Chicago, Ill.* Fourteen dogs have been exposed for 40 hours per week to the vapors of commercial benzene at a concentration of 600 p.p.m. by volume. Diets of known composition were fed in which the fat or protein content was varied. The four diets fed were: (1) High protein (2 gms./lb. body wt.)–High fat (33 per cent); (2) High protein–Low fat (15 per cent); (3) Low protein (1 gm./lb. body wt.)–High fat; (4) Low protein–Low fat. The criteria used to determine the susceptibility of the dogs to benzene fumes were: survival time, degree of leucopenia, percentage conjugation of urine sulphates, liver function (Rose Bengal Dye Clearance), red blood cell and platelets counts. The results indicate that animals receiving the low protein diet are much more susceptible to benzene fumes than are animals on a high protein diet. No definite conclusion has been drawn as to effect of dietary fat on susceptibility to benzene. The changes observed in exposed animals on the low protein diet occurred with a rapidity and severity which control studies prove could not be attributed to the diet alone. Seven animals receiving the low protein diet have succumbed to the benzene fumes after an average exposure of 14 weeks. Two low protein animals are alive at the present time after 23 and 11 weeks of exposure respectively. Two of the high protein animals have died, one survived 50 weeks, the other 43 weeks; while two animals on this diet are still alive after 52 and 23 weeks of exposure respectively. [*This study was assisted by a grant from the Velsicol Corporation.*]

Effect of heparin on growth of lupinus albus. DAVID I. MACHT. *Pharmacological Research Lab., Hynson, Westcott & Dunning, Inc., Baltimore, Md.* The effect of various concentrations of heparin was studied on root growth of *Lupinus albus* seedlings, large variety. Control seedlings were grown in Shive plant-physiological solution according to the author's technique (described elsewhere) in the dark at 20°C. Other seedlings from the same crop and under exactly the same ecological conditions were grown in heparin solutions ranging from 1:5,000 to 1:100,000 in concentration. Results of numerous experiments with each concentration revealed a peculiar growth curve. Certain concentrations of heparin stimulated root growth while others definitely inhibited it. Thus, concentrations of 1:20,000, 1:50,000, 1:80,000 and 1:100,000, respectively gave 108, 120, 110 and 110 per cent as indices of growth. On the other hand, concentrations of 1:30,000 and 1:70,000 gave a phytotoxic index of 70 and of 75 per cent, respectively. This phytopharmacological phenomenon was obtained with all makes of heparin examined. On the other hand, experiments with sodium salt of polyanethole sulphuric acid, a synthetic homologue of heparin, revealed no such growth-stimulating action but inhibited growth in all the concentrations examined.

Influence of sulfanilamide and para-amino benzoic acid on frogs' eggs and larvae. DAVID I. MACHT. *Pharmacological Research Lab., Hynson, Westcott, & Dunning, Inc., Baltimore, Md.* Fertilized eggs of *Rana sylvatica* were placed in solutions of various concentrations of sulfanilamide and para-amino benzoic acid to ascertain their effect on the development and growth of tadpoles. In solutions ranging from 1:5,000 to 1:2,000 sulfanilamide was not very poisonous for frogs' eggs but para-amino benzoic acid, or Paba, killed them. Combinations of sulfanilamide and Paba acted synergistically, i.e., exerted more toxicity than could be explained by adding their respective effects. Tadpoles from 3 to 21 days old were also not much affected by sulfanilamide. Thus, concentrations of 1:1,000 of sulfanilamide were not fatal. On the other hand, a solution of Paba, 1:1,000, produced death. The toxicity of Paba was due not to its pH but to an intrinsic effect of the molecule. Combinations of the two drugs also exerted a synergistic action on tadpoles from 2 to 4 days old. On larger tadpoles, 3 weeks old, the synergistic action was not so pronounced.

The toxicity of duponal for living tissues. DAVID I. MACHT. *Pharmacological Research Lab., Hynson, Westcott & Dunning, Inc., Baltimore, Md.* An inquiry was made into the effects of "Duponal" (sodium lauryl sulphate) on rabbits, guinea pigs, rats and mice. Subcutaneous and intramuscular injections of 0.1 per cent solutions in water and saline destroyed the tissues injected. Even 1 c.c. of a 0.01 per cent solution produced definite necrotic changes at site of injection. Applications to the surface of the skin and mucous membranes were not very irritating. However, instillation into the conjunctival sac of cats and rabbits produced irritation and reddening. Intraperitoneal injections of a 0.01 per cent solution in mice were fatal. Intravenous injection of as much as 5 c.c. of a 0.1 per cent solution was not dangerous but produced a fall in blood pressure and depression of the respiration.

Toxicity of cobra neurotoxin for previously treated mice. DAVID I. MACHT. *Pharmacological Research Lab., Hynson, Westcott & Dunning, Inc., Baltimore, Md.* The solution of cobra venom (H. W. & D.) employed consisted almost entirely of cobra neurotoxin, $m.l.d._{66}$. Six series of mice were re-

peatedly studied. The first series, made up of controls, gave m.l.d.$_{48}$. A second series of mice was injected with sublethal doses of digitalis tincture after evaporating the alcohol and replacing its volume with physiological saline. A week or more after recovery from the digitalis poisoning, the mice were injected with the neurotoxin solution. In this series the cobra venom produced less mortality than it did in the control mice. A third series of mice was poisoned with $HgCl_2$ in saline (0.01 c.c. per gram weight), a dose producing many deaths. The surviving animals, exhibiting definite nephritic histological changes, were injected with cobra venom a week or two later. There was no increase in mortality of these mice due to kidney injury as compared with the controls. The fourth series of mice recovered from injections of sulfanilamide, 5 c.c. of 0.5 per cent solution and of pontosil, 1 per cent. Subsequent injections of cobra venom did not increase mortality rate of the fourth series. Sublethal doses of cobra venom were injected in mice of the fifth series. Subsequent injection of standardized cobra venom greatly increased the mortality rate. In the sixth series of mice studies were made on the relation of cobra venom to thiamin. Mice raised on a thiamin-deficient diet succumbed to cobra venom more quickly than the controls. On the other hand, injections of 1 to 2 mg. of thiamin for three successive days reduced mortality as much as 50 per cent. The results of the experiments described above indicate that cobra neurotoxin does not injure either heart or kidney but is a specific neurological poison.

The effect of anoxia on fat absorption in rats. P. L. MacLachlan and C. Woodrow Thacker (introduced by E. J. Van Liere). Albino rats of both sexes, weighing about 200 gm. each, were fasted 48 hours and given 1.5 cc. of corn oil (1.385 ±0.01 gm.) by stomach tube under light ether anaesthesia. After fully recovering consciousness (1–2 minutes) the experimental rats were subjected to a reduced pressure of 254 mm. of Hg. (equivalent to an oxygen tension of 7.03 per cent) in a specially constructed steel respiratory chamber. Controls were kept at atmospheric pressure. Four hours after feeding, the amount of unabsorbed fat in the stomach, small intestine and caecum was quantitatively determined and the value obtained used to calculate the percentage absorption, correction being made for the fat present in the fasted gut.

The average amount of fat absorbed (31.8 per cent) by ten rats subjected to low oxygen tension was significantly less than that absorbed (57.1 per cent) by ten control rats; the P value (Fisher) was less than 0.001.

Experiments are in progress to determine the threshold of fat absorption by subjecting rats to various oxygen tensions. It is also planned to determine the effect on fat absorption of pressures lower than 254 mm. of Hg.

The negative intrapleural pressure: "Cart before the horse." N. S. Rustum Maluf. *School of Medicine, Georgetown Univ., Washington, D. C., and Harvard Medical School.* Standard physiological text-books state that the negative intrapleural pressure determines pulmonary expansion. We present models and actual experiments on live animals showing that the negative intrapleural pressure does not determine pulmonary expansion except in pneumothorax. The negative intrapleural pressure is merely the *result* of the retractile tension of the lungs.

The factor which maintains the undiminished expansion of an elastic bag surrounded by liquid without a free surface is the tensile strength of the liquid. The bag surrounded by air will yield somewhat when it produces a negative pressure about itself by its retractile force; the bag surrounded by liquid without a free surface will not yield at all. Evacuating the lungs of an animal will not cause any pulmonary collapse, unless the lungs are torn. The same applies when a vacuum is simultaneously produced both inside of the lungs and external to the chest (Roth's experiment). The lungs are held to the thorax, including the diaphragm, by a liquid with a high tensile strength. We described a model which demonstrates pulmonary mechanics with the above physical facts considered.

Brauer and Roth and others who have gone to the other extreme by denying the existence of a negative intrapleural pressure on the basis of the high tensile strength of water, confused two different phenomena: (1) tensile strength, which is relatively constant and merely states the strain at rupture when no free surface is present, and (2) the forces which cause fluids to flow—hydrostatic and atmospheric pressure.

The absence of pleural clefts in certain mammals: a theory of its mechanical significance. N. S. Rustum Maluf. *Harvard Medical School.* It has been known for long that elephants, whales, and dolphins have no pleural clefts. Dense connective tissue unites the visceral and parietal pleurae.

I submit the following statements for mammals with obliterated pleural clefts: (1) Gliding (shearing) movements of the lungs against the thorax, which occur in other mammals but are of course impossible in these, are no longer necessary because ventilation of the pulmonary apices is no longer a problem and the diaphragmatic surface of the lungs is greatly preponderant. (2) The parietal and visceral pleurae can therefore afford to be united by actual tissue; it becomes no more necessary to run the imminent risk of pneumothorax whenever the lungs are torn. (3) *The sudden great changes in volume which the lungs of these mammals*

undergo probably would not otherwise be possible because of the danger of pneumothorax resulting from pulmonary rupture. In the whales and dolphins, brisk rises to the surface must produce sudden pulmonary distension because their thoracic cage is incomplete and thus relatively plastic to changes in hydrostatic pressure. When drinking, elephants inhale several liters of water through their long narrow trunk and then exhale it into their mouth under considerable pressure; the whole process takes only a few seconds and involves sudden large changes in pulmonary volume with steep fluctuations in intrapulmonary pressure.

Incidentally, these animals can have no negative intrapleural pressure because the retractile tension of their lungs is exerted directly on the thorax and diaphragm and not on an intrapleural fluid.

Studies on the detoxification of barbiturates. G. MASSON and E. BELAND (introduced by H. Selye). *Dept. of Anatomy, McGill Univ., Montreal, Canada.* In order to establish the site of detoxification of barbiturates in the body, we determined the duration of anesthesia produced by various barbiturates in intact, completely nephrectomized or partially hepatectomized (75% of the liver removed) rats under identical conditions. Since in the absence of detoxifying tissue the activity of these anesthetics is prolonged, it was possible thus to estimate what proportion of each of these compounds is detoxified by hepatic, renal and other tissues of the body. From the data obtained with twenty-five compounds, barbiturates can be classified into four groups. Group I: Those mainly detoxified in the kidney (e.g. barbital). Group II: Those mainly detoxified in the liver (e.g. ipral, amytal, nembutal, ortal, phenobarbital, alurate, nostal, seconal, allyl-pental, evipal, thioethamyl, sec. hexyl-ethyl, l-methyl-allyl-isobutyl, l-methyl-propylcrotyl and n-allyl-l-methyl-butyl-ethyl barbiturates. Group III: Those approximately equally detoxified in the liver and kidney (e.g., neonal, delvinal, phanodorn, dial). Group IV: Those possibly detoxified in other tissues of the body, but not to any great extent in liver or kidney (pentothal, l-methyl-allyl-propyl and l-methyl-allyl-allyl thiobarbiturates).

The effect on metabolism of iodination of protein under conditions compatible with life. J. F. MCCLENDON and WM. C. FOSTER (by invitation). *Research Lab. of Physiology, Hahnemann Medical College, Phila.* Since Bliakher and Belkin as well as Uhlenhuth and Winter showed that a crystal of iodine implanted in a hypophysectomized axolotl would cause it to metamorphose, and since the axolotl might contain thyroglobulin of low metabolic activity capable of being increased by iodination, iodination of thyroglobulin under conditions compatible with life was studied. Rats of about 170 grams in weight were selected and found to have a basal metabolic rate (B.M.R.) averaging 30 calories per square meter of body surface per hr. under light delvinal anesthesia. One rat was fed half a gram of dry thyroglobulin from a goiter and its B.M.R. on the 2nd, 5th and 7th day found to average 41.17 calories per square meter per hour.

Another portion of this thyroglobulin was dissolved in bicarbonate-containing, physiological salt solution and stirred with iodine crystals for 20 hours at body temperature, then freed from inorganic impurities and dried. One half gram was fed to a similar rat and the B.M.R. on the 2nd, 4th and 7th day was found to average 44.2 calories per square meter per hour. The increase of more than 3 calories was evidently due to the iodination of the protein under conditions similar to those surrounding the crystal implanted in the axolotl. Such a process may have accounted for the metamorphosis.

Rate of absorption of acetate by the gut and transformation in the liver. J. F. MCCLENDON and JOHN SCOTT. *Research Lab. of Physiology, Hahnemann Medical College, Phila.* Absorption of acetate increases the volatile fatty acid (VFA) in the blood, which is expressed in terms of cc. of 0.01 *N* CO_2-free NaOH neutralizing the CO_2-free distillate of 100 cc. of blood by the method of McClendon (Federation Proceedings **2**: 66, 1943). After injection of 100 cc. 0.2 *N* sodium acetate into the duodenum, the VFA in the portal vein rose in 4 minutes (from a basal level of 3) to 21. At the 12th. minute it was 13 and 16th. minute 11. It dropped by the 50th. minute to 4 and remained constant until by the 120th. minute, then dropped by the 160th. minute to the basal level of 3 (when it was the same in the hepatic and iliac veins). The VFA in the iliac artery rose (from a basal level of 3) by the 13th. minute to 4 and remained constant until the 24th. minute then dropped by the 56th. minute to 3. The VFA in the iliac vein remained constant at 3 for the entire period.

When 50 cc. of 0.2 *N* acetate was injected into the right iliac vein the VFA rose in the left iliac vein within 1 minute to 24, then returned within 10 minutes to the basal level of 3.

When 2 liters of 0.2 *N* acetate was injected into the right iliac vein continuously at the rate of 4 cc. per minute the VFA in the left iliac vein increased to 4, at 7 cc. per minute the VFA was 7, at 8 cc. per minute the VFA was 9 and at 14 cc. per minute the VFA was 38 and there was a marked increase in the amplitude of the rhythmic contractions of the duodenum as registered by the balloon method.

Since the acetate was trapped by the liver, this is in accord with the belief that it is metabolized although not transformed into glucose.

A simplified test for the presence of necrosin in various body fluids. VALY MENKIN. *Fearing*

Research Lab., Free Hospital for Women, Brookline, Mass. Earlier studies by the writer have indicated that severely injured cells release into inflammatory exudates a substance capable of accounting for the basic pattern of injury in inflammation (Arch. Path. **36**: 269, 1943). This substance, which is associated with the euglobulin fraction of exudates, seems to be an atypical euglobulin, i.e., if it proves to be a euglobulin at all. For instance, in contrast to typical euglobulins, this substance, termed necrosin, fails to be dissolved by the presence of Na Cl. Necrosin has been shown to induce fever and as such it seems to be the only fraction of exudates capable of inducing this type of reaction (Proc. Soc. Exper. Biol. and Med. **54**: 184, 1943). This observation may throw further light on the exact mechanism of fever formation with inflammatory processes. Further studies indicate that not only the dog develops an elevation in temperature by the intravascular injection of necrosin, but that the rabbit is likewise extremely sensitive in developing fever upon the intravenous injection of necrosin. The temperature may become elevated from one to several degrees Fahrenheit within a very few hours following the introduction of the substance. This pyrogenic reaction in the rabbit seems to be so specific as to render it conceivable that this animal may be well used for the testing of necrosin in various body fluids. [*Supported by a grant from the Johnson & Johnson Research Foundation, New Brunswick, New Jersey; and also by a grant from the Dazian Foundation for Medical Research.*]

Effects of bilateral, simultaneous ablation of area 4, area 6 and areas 4 and 6 from the simian cerebral cortex. FRED A. METTLER. *Dept. of Neurology, College of Physicians and Surgeons, Columbia Univ.* Bilateral removal of area 4 immediately produces marked sensitivity to labyrinthine and proprioceptive righting reflexes and resistance to passive movements which oppose these reflexes. While the sensitivity diminishes and the animal learns to walk, the legs continue to be somewhat internally rotated and adducted and the toes extended and abducted. Extensor movements continue to be exaggerated. Mastication, fine digital and extreme degrees of large muscle movement are acutely abolished and chronically impaired. Plantar response becomes difficult to elicit, threshold of patellar reflex is raised, response is brisk and reflexogenous zone is restricted. None of these phenomena are related to damage of area 6 and such damage does not produce, either primarily or secondarily, any resistance, or increase in resistance, to passive movement. A phase I grasp reflex can be reliably elicited after bilateral 6 removal and a phase I response is also seen after bilateral, simultaneous removal of 4 and 6. Bilateral 6 removal produces pronounced but temporary manual apraxia, spontaneous ambulatory overactivity (bilateral removal of Walker's area 13 cortex without other damage has no effect upon the kinetic state), irregular plantar responses, slight rise in patellar reflex threshold and spreading of this reflex. Stiffness after area 4 removal is result of removal of 4S (which lies in area 4, not between it and 6) and has nothing to do with area 6. Removal of caudal parts of area 4 abolishes primate manual feeding pattern but hands are not paralysed and are used in infraprimate patterns.

Effect of parathyroid removal on the serum calcium and inorganic phosphorus of nephrectomized dogs. E. P. MONAHAN (by invitation) and SMITH FREEMAN. *Dept. of Physiology, Northwestern Univ. Medical School, Chicago, Ill.* It has been proposed that the parathyroid gland affects the level of serum calcium by virtue of its effect on the excretion of phosphorus by the kidney.

Fifteen large (20 kilo.), adult dogs were bilaterally nephrectomized. Eight of the animals had a total thyroparathyroidectomy at the time of nephrectomy. Studies were made of the serum calcium, serum inorganic phosphate, alkaline serum phosphatase, and the non-protein nitrogen. Determinations were made immediately prior to operation, 12 hours following, and at 24 hour intervals thereafter.

The average survival time of the animals undergoing parathyroidectomy was 74 hours, while average survival of the animals having only the kidneys removed was 95 hours.

The serum calcium values of the nephrectomized dogs remained within normal limits (11.0–10.2 mgs. per cent), while the serum calcium of the thyroparathyroidectomized group was depressed from an average control value of 11.3 mgs. per cent to an average value of 5.9 mgs. per cent in an interval of 72 hours.

The serum inorganic phosphate of both groups of animals was greatly elevated. For the nephrectomized group the average value in 72 hours was 25.6 mgs. per cent, an increase of 21 mgs. per cent. The animals with nephrectomy and thyroparathyroidectomy averaged 17.1 mgs. per cent within the same period, an increase of 13.3 mgs. per cent.

The marked difference in the behavior of the serum calcium in the two groups of animals, in spite of a similar elevation of the serum inorganic phosphorus, indicates that the parathyroid gland exerts a direct effect in maintaining the serum calcium level, which is not dependent upon kidney function.

Electrical conductivity in plasmodium as affected by comminution and heat death. A. R. MOORE and P. VAN RYSSELBERGHE (by invitation). *Depts. of Psychology and Chemistry of the Univ. of Oregon, Eugene.* Plasmodium polycephalum grown on

Cohen's medium supplied the living substance which was collected from the sides of the culture vessels. The material was put into a glass cell provided with movable needle platinum electrodes placed vertically 11 mm. apart. After the substance (8 cc.) was packed in place, the electrodes were plunged in and secured. Cell constant = 0.565. Readings were made with the vessel in an oil bath at 25°C. In series 1 the culture medium was made up with tap water, in series 2 with dilute Ringer = approximately M/32 NaCl. Conductance was determined for 3 conditions of the plasmodium; gently pressed into the cell, comminuted by forcing through silk gauze of pore size 0.2 mm., killed by heating in boiling water for a few minutes.

Specific conductance of Plasmodium

	Culture medium	Normal	Comminuted	Heat killed
Series 1	0.000767	0.001738	0.002224	0.002404
Series 2	0.003580	0.002637	0.003025	0.003215

The results consistently show an increase of conductance on comminution, still further with heat death. This suggests that formed elements are responsible for maintaining some of the electrical resistance. Comminution to 0.2 mm. partially destroys this resistance and heat death carries the process farther. An increase in the conductance of the medium results in an increase in that of the plasmodium grown on it.

The effect of certain vitamins experimental in renal hypertension. W. G. Moss (by invitation) and G. E. WAKERLIN. *Dept. of Physiology, Univ. of Illinois College of Medicine.* Unquestionably the hypertensive effect of the Goldblatt kidney in experimental renal hypertension involves some change in the metabolism of the renal cells. Vitamins are well-known to constitute part of cellular enzyme systems or otherwise to influence cellular metabolism. Consequently we studied the effect of certain vitamins by mouth in experimental renal hypertension. Moreover therapeutic effects in essential hypertension have been claimed for certain vitamins (A, B complex and C).

Three hypertensive dogs treated with one lot of a particular vitamin A concentrate (200,000 units per day for three months followed by 400,000 units per day for an additional three months) showed striking reductions in blood pressures. These reductions were later shown to have been due to some component of the preparation other than vitamin A since three other lots of the same vitamin A concentrate were without antihypertensive effect in four hypertensive dogs. We are now studying various fish liver oil and fish oil fractions in an effort to obtain this orally effective antihypertensive substance.

One dog treated with a vitamin B complex concentrate (containing thiamin 0.15 mgm., riboflavin .01 mgm., pyridoxine 0.15 mgm., nicotinic acid 2 mgm., and pantothenic acid 0.4 mgm. per cc.) in a dose of 8 cc. per day for six weeks followed by 12 cc. per day for an additional four weeks showed no reduction in blood pressure. One dog treated with ascorbic acid in a dose of 1 gm. per day for a period of four months showed no change in blood pressure. One dog treated with vitamin E in a daily dose of 100 mgm. of mixed tocopherols (equal inactivity to 60 mgm. of alpha-tocopherol) for five months showed no reduction in blood pressure. [*Aided by a grant from the Winthrop Chemical Company.*]

Repeated exposure to simulated high altitude: estrus cycles and fertility of the white rat. DOROTHY NELSON and M. W. BURRILL (introduced by A. C. Ivy). *Dept. of Physiology, Northwestern Univ. Medical School, Chicago, Ill.* Ten young adult females with normal cycles (established by daily vaginal smears for 23 days) were exposed in a low pressure chamber to a simulated altitude of 18,000 feet, 1 hour daily for varying lengths of time (2-5 months). Daily smearings during the exposure period showed only the slight irregularities in the duration of the various phases of the cycle generally found in normal animals. There was no tendency, even in the rats exposed for 5 months toward prolonged estrus or anestrus. Eight of the 10 females became pregnant after exposure was discontinued. The two which did not become pregnant had been exposed for four months. However 3 others exposed for a longer time (5 months) did become pregnant, so it is concluded that repeated exposure to anoxia, to the degree used in these experiments, does not interfere with the reproductive physiology of the white rat and does not reduce fertility. [*This study was assisted by a grant from the Clara L. Abbott Fund.*]

Repeated exposure to simulated high altitude: weights of adrenals, testes and seminal vesicles in the white rat. DOROTHY NELSON and M. W. BURRILL (introduced by A. C. Ivy). *Dept. of Physiology, Northwestern Univ. Medical School, Chicago, Ill.* A group of 19 adult male white rats was exposed to reduced pressure (equivalent to an altitude of 18,000 feet) 1 hour daily for 50 days. The weights of the testes, seminal vesicles and adrenals were compared with the organ weights of a control group of 21 animals. The average body weights of the two groups were equivalent at the start, but the control group gained slightly more during the experimental period (final average weights: experimental 221 gm., control 248 gms.). There was no difference between the two groups in the weights of the testes and adrenals even when compared on the basis of organ weight/body weight ratio. The seminal vesicles of the exposed

rats, although smaller than the controls, were not significantly different when compared on the basis of organ weight/body weight ratio.

In an experiment involving more drastic exposure for shorter total periods, Tornetta et al (Proceedings 1943) found significant changes in the weights of seminal vesicles, testes (decreased) and adrenals (increased). Evidently a more chronic but less intensive exposure to anoxia, as in the present experiment, fails to produce the same changes. [*This study was assisted by a grant from the Clara L. Abbott Fund.*]

Sensations arising during the passage of a constant galvanic current. ERIC OGDEN. *Univ. of Texas Medical Branch, Galveston* and CHARLES F. DALZIEL (by invitation). *Univ. of California, Dept. of Electrical Engineering, Berkeley.* While direct currents up to 83 m.a. were passing through the palm, wrist, and forearm in experiments on electrical safety, (Dalziel, Ogden, and Abbott, Electrical Engineering **62:** 745, 1943) two sensations appeared. The first, the well known tingling at the electrode, is probably due to polarization and becomes burning pain at high current densities. But the other, a severe deep burning or aching sensation at the wrist, appears to conflict with the classical concept that a constant current, though modifying excitability does not excite except at make or break, and thus conflicts with the du Bois Reymond law of excitation.

Both heat sensations might be due to heat production. A simple calculation shows that this is unlikely. Heat near electrode = $0.24I^2R$ (I = current, R = resistance of contact and skin tissues). Taking I = 50 m.a. R = 500 ω, Heat = 0.3 cal/sec. With a contact area of 125 Cm^2 (the flat palm) only 0.0024 cal/Cm^2/sec would be available for overcoming the thermo-stabilising effect of the blood stream and exciting the heat receptors. Similar considerations apply to the interelectrode liberation of heat and suggest that this is not adequate to produce the sensation at the wrist.

Cutaneous vasodilatation, almost certainly present in these circumstances, might explain the hot sensations though vasodilatation without congestion gives rise to sensations of warmth rather than burning since the blood temperature is the limiting factor. Perhaps a high current density is developed in the nerve trunks in the wrist and the particular sensation evoked depends upon the specific connections of those fibers which are most susceptible to this kind of stimulus.

Simultaneous diabetogenic and nitrogen sparing action of anterior pituitary extract in partially depancreatized rats. K. E. PASCHKIS, A. CANTAROW and A. E. RAKOFF (by invitation). *Jefferson Medical College and Hospital, Philadelphia, Pa.* A close relationship of the protein-anabolizing (growth) hormone to the diabetogenic factor of the anterior pituitary has been claimed. It has been suggested that an anterior pituitary extract (A.P.E.) is protein-anabolizing through stimulation of insulin secretion and diabetogenic if the islets are incapable of responding to the stimulus.

Fifteen partially depancreatized rats were treated with a growth-promoting A.P.E. (Antuitrin G). In 10 rats the extract was diabetogenic, inducing glycosuria in rats in which the diabetes had been latent or increasing glycosuria present before treatment with the extract. The diabetogenic action was transient and did not persist beyond the period of treatment, which varied from 3 to 14 days. None of the rats showed increased nitrogen excretion during the period of exacerbation of the diabetes, and in six nitrogen retention occurred during this period.

The simultaneous occurrence of nitrogen retention and exacerbation of diabetes militates against the theory that the protein-anabolizing (nitrogen sparing) action of A.P.E. is due to stimulation of insulin secretion which in turn would cause protein anabolism. Amounts of insulin secreted by the pancreatic remnants in the partially depancreatized rat must be small at best since they are inadequate to counteract the diabetogenic effect of A.P.E. The decreased nitrogen excretion observed in the experiments could be attributed to insulin secretion only if one wished to assume that much smaller amounts of insulin were necessary to influence protein metabolism that are capable of increasing carbohydrate utilization.

The stabilization of cytochrome C by lyophilization. ELIZABETH A. PATCH (by invitation), HELEN S. MORRISON (by invitation), JOSEPH L. CIMINERA (by invitation) and KARL H. BEYER. *The Dept. of Pharmacology, Medical-Research Division, Sharp and Dohme, Inc., Glenolden, Pa.* Cytochrome C was prepared from beef heart essentially by the method of Keilin and Hartree (Proc. Roy. Soc. London, **B122:** p. 298, 1937). Aliquots of the final clear solution were pipetted into ampoules, frozen and dried under reduced pressure (lyophile process). The ampoules were sealed under reduced pressure and stored in a refrigerator.

The lyophilized preparation was very pale tan to pink in color, very light and feathery, and restored completely on the addition of distilled water to give a clear dark red solution. Thus it was possible to restore the material to give a desired concentration suitable for Warburg studies.

The lyophilized cytochrome C was assayed immediately after ampouling by restoring to a given volume and comparing it to cytochrome C from the same lot which had been kept as a stock solution. Spectrophotometrically, the concentration of cytochrome C was determined at a wave length of 550 mμ according to the formula $C = E$, where E = absorption coefficient of reduced or oxidized

cytochrome. Over a period of four months there was no decrease in the concentration of either phase of the enzyme nor any change in their spectral characteristics.

Using the concentration of cytochrome C as the limiting factor in the determination of the rate of oxidation of succinate by the complete succinoxidase system, it was found that equal concentrations of fresh stock solution and restored cytochrome C gave the same rates of oxygen uptake. Lyophilized cytochrome C four months old had the same activity, when diluted to the same concentrations, as when originally prepared.

The distention pressure of urine in the bladder as it influences human gastric motility. T. L. PATTERSON and D. J. SANDWEISS (by invitation). *Dept. of Physiology, Wayne Univ., College of Medicine, Detroit, Mich.* Incident to a series of graphic observations on the effects of urine extracts on the motility of the empty stomach of a young woman with a permanent gastric fistula (balloon method was employed for registration), it was additionally observed, that when the intra-urinary distention pressure caused by the gradual accumulation of urine in the bladder reached a pressure level sufficient to arouse the micturition reflex, definite alterations in the gastric motility usually began to occur. At first, the gastric contractions became more or less irregularly spaced with fluctuations in the gastric tonus. Then, as the condition became more pronounced through voluntary inhibition, the subject exhibited restlessness leading to increased intervals of rest between the individual contractions, or groups of contractions, reduction in amplitude of contractions and finally inhibition when the distress approached the level of pain.

In a few minutes following the evacuation of the bladder the normal gastric contractions were resumed and the patient was again at ease.

These results are in confirmation with the earlier findings of Patterson and Dunn on fistularized stomach and bladder dogs (Proc. Am. J. Physiol. **133:** 410, 1941), in which rubber balloons were introduced into the urinary bladder and the stomach, respectively, for synchronously recording the gastric motility and distension pressures employed in the bladder.

The renal elimination of sulfamerazine (2-sulfanilamido-4-methyl pyrimidine) by the dog. LAWRENCE PETERS (by invitation), KARL H. BEYER and ELIZABETH A. PATCH (by invitation). *From the Dept. of Pharmacology, Medical-Research Division, Sharp and Dohme, Inc., Glenolden, Pa.* We have studied the renal elimination of sulfamerazine under conditions that may exist or be produced during sulfonamide therapy. Attention was also given to creatinine clearance ratios as influenced by plasma protein binding of sulfamerazine.

Sufficient bicarbonate administered orally to increase urinary pH from 6.8 to 7.8 in 3 dogs increased the clearance of sulfamerazine from 7.3, 6.4, and 7.6 to 14.9, 22.3 and 19.6, respectively. This was very likely due for the most part to increased electrolyte excretion rather than to pH change for an equivalent amount of NaCl, KCl or NH_4Cl produced a similar but not as great effect. Increase in urine flow from 0.42–2.82, 0.29–5.75, 0.24–4.90 cc./min. increased sulfonamide clearance from 5.9–11.4, 5.0–17.4, 5.2–11.2, respectively. The clearance of sulfamerazine remained fairly constant when the plasma level was increased from 3.4 to 13.1 mgm./100 cc. during individual experiments indicating that maximal tubular resorption of the compound was not exceeded. Following bicarbonate administration (urinary pH = 8), increasing the plasma sulfonamide from 4 to 13 mgm./100 cc. increased sulfamerazine clearance about 50 per cent. The clearance ratio of sulfamerazine (4 mgm./100 cc. plasma) to creatinine was normally 0.13; corrected for plasma binding the excretion ratio of sulfamerazine to creatinine was 0.20.

Assuming complete glomerular filtration of unbound sulfamerazine these data indicate that normally about 80 per cent of the filtered compound is resorbed by the renal tubules of the dog.

The nature of the renal vascular reactions to amino acid infusion. R. F. PITTS. *Dept. of Physiology, Cornell Medical College, New York, N. Y.* The nature of the hemodynamic changes produced in the kidney of the normal dog on administration of amino acid (Pitts, Am. J. Physiol. **140:** 156; 1943) has been studied by the simultaneous measurement of the creatinine clearance (glomerular filtration rate), p-amino hippuric acid clearance (minimum effective renal plasma flow), hematocrit and mean arterial pressure. From the data so obtained the renal blood flow and total renal resistance have been calculated. Gradual elevation of plasma amino nitrogen from a normal of about 4 mgm. per cent to 20 mgm. per cent by the infusion of glycin led to an increase in filtration rate and renal blood flow with some decline in filtration fraction. Mean arterial pressure either remained constant or increased moderately. Total renal resistance declined sharply in all instances. The nature and extent of these changes indicate that amino acid either directly or indirectly brings about a dilation of the renal vascular bed. The dilation affects both pre- and postglomerular vessels. In experiments in which the plasma amino nitrogen concentration was raised to 50 to 60 mgm. per cent there occurred a decline in filtration rate and renal blood flow and an increase in filtration fraction and renal resistance. These

changes result from constriction of both pre- and postglomerular vessels.

The renal reabsorption of inorganic phosphate in the normal dog. R. F. PITTS and R. S. ALEXANDER (by invitation). *Dept. of Physiology, Cornell Medical College, New York, N. Y.* The renal reabsorption of inorganic phosphate has been studied in the dog over a range of plasma concentration from 2 to 50 mgm. per cent of phosphate phosphorous, using the simultaneously determined creatinine clearance as a measure of glomerular filtration rate. The quantity of phosphate reabsorbed is essentially independent of plasma concentration over a range from 10 to 50 mgm. per cent, and in two dogs amounted on an average to 4.5 mgm. per minute. At plasma concentrations of less than 3 mgm. per cent all phosphate was reabsorbed from the glomerular filtrate and the urines were essentially phosphate free. With plasma concentrations of 3 to 10 mgm. per cent the reabsorption of phosphate may increase slightly as a function of plasma concentration. At levels above 6 mgm. per cent there was considerable fluctuation in the amount of phosphate reabsorbed in different experiments, although all values fell within the limits of 3.5 and 5.0 mgm. per minute. It is possible that these fluctuations in reabsorptive capacity for phosphate may be correlated with variations in acid base balance or with general electrolyte balance on different experimental days.

Spinal reflex summation as a possible clue to the conditions underlying paroxysmal pain in causalgia. E. L. PORTER. *Dept. of Physiology, Medical Branch, Univ. of Texas, Galveston.* In the condition known as "Causalgia" the constant low grade pain may be increased to an unbearable point by additional stimuli such as drying of the skin, slight friction, cold and the like of which the normal individual would scarcely be aware. There is a strong resemblance to summation as seen in spinal reflexes. In a spinal cat carefully controlled stimulation of a cut sensory nerve is arranged to give rhythmic reflex contractions of the tibialis anticus muscle of nearly minimal extent. Additional stimuli imitating those effective in causalgia are now given to different areas of the leg. If summation occurs following the extra stimulus the contraction heights rise suddenly to perhaps 10 times the original. That the phenomenon is a true summation is shown by the fact that cessation of electrical stimulus to the nerve results in quiescence of the muscle even though the extra mechanical stimulus to the leg is being continued as strongly as before. Extra stimuli which have been found effective in causing summation in this way are: rubbing the fur of knee or foot with a wooden applicator, spreading the toes strongly, application of a bull-dog clamp to a toe pad, twisting a claw, a strong blast of air on fur of foot or knee, in some cases even blowing the breath on such areas.

These observations suggest that the summation of stimuli in causalgia resulting in unbearable pain may not occur primarily in consciousness, but in some lower center in the nervous system.

A pendulum time-marker for universal driving current. F. H. PRATT. *Physiological Lab., Boston Univ. School of Medicine.* A cylindrical Hg-Hg commercial switch, adjustable in angle, is mounted just below the pivot, obviating the frictional resistance of a solid-metallic contact mechanism. Two polar-opposed electromagnets, one forming the bob, the other embedded centrally in the base, provide at mid-swing an impetus of temporal and mechanical advantage. The circuit draws as little as 0.3 ampere. This disposition and economy of current permits the use equally well of one standard ½ volt dry cell, a d.c. line with simple 2-lamp shunt resistance, or *unrectified a.c.* from an inexpensive 6-10 volt bell-ringing transformer. The atter, with plug-connection for a lighting circuit, is mounted as an integral part of the set-up and operates indefinitely without attention. Regulation is afforded by a sliding weight on the pendulum-rod. The pendulum actuates the usual relay, selective for a variety of time intervals. The device is thus adaptable to laboratory installations with widely differing facilities.

The motor activity of the pyloric sphincter studied by the pyloric inductograph. J. P. QUIGLEY and DANIEL A. BRODY (by invitation). *Dept. of Physiology, Western Reserve Univ. Medical School, Cleveland, Ohio.* In this investigation, the pyloric sphincter movements have been studied by two small electromagnetic coils. These coils were attached to the serosal surface directly above and below the sphincter so they move closer or farther apart by contractions or relaxations respectively of the sphincter. Lead wires conduct the current into one coil (the primary) and this induces a magnitude of current in the secondary coil, which varies as the distance between coils. The current from the secondary coil is passed through a radio amplifier and then recorded by an oscillograph and photokymograph. When this apparatus is applied to the sphincter it is termed a "pyloric inductograph," but in a modified form it is capable of extensive application in studying the movement of many tissues. It provides a continuous record from the unanesthetized, untraumatized animal under essentially physiological conditions.

Extensive studies with this technic have demonstrated that the pyloric sphincter of the fasting dog usually exhibits rhythmic contractions at the rate of 4–6 per minute. For brief intervals, these movements may be absent and at such times the

sphincter is relaxed. In general, the sphincter is open more than half the time.

Similar activity obtains in the fed animal but the frequency and magnitude of the contractions are slightly greater and quiescent periods are rare. Studies with the pyloric inductograph made simultaneously with fluoroscopic observations of the evacuation of a barium meal show that each cycle of gastric evacuation begins shortly after the sphincter is fully relaxed and continues until the peak of the sphincter contraction. [*This investigation was partially supported by a research grant from the Council on Pharmacy and Chemistry of the American Medical Association.*]

The clearance of injected estrogens from the blood of normal humans and dogs and those with liver damage. A. E. RAKOFF (by invitation), A. CANTAROW, K. E. PASCHKIS and L. P. HANSEN (by invitation). *Jefferson Medical College and Hospital, Philadelphia, Pa.* Free serum estrogen was determined (Fluhman method) in dogs and humans (normal and liver-damage) after administration of estrogens.

Dog Experiments: Eleven dogs, 5 with bile-fistulas, received estrogens intravenously in alcohol, estradiol in 7 experiments, estrone in 3 and diethylstilbestrol in 1, usually 250,000 i.u. In 4 normal dogs the highest values were obtained at 5 or 10 minutes and ranged from 320–2500 i.u. per 100 cc., fell progressively at 1 and 5 hours, and none was demonstrable at 24 hours. In 3 dogs with acute CC14 poisoning the curves were abnormal in 2; in one the estrogen gradually increased to a maximum at 48 hours, while in the other, although the curve fell during the first 24 hours, an increase occurred at 48 hours. In 2 dogs with chronic CC14 poisoning, clearance was prolonged, but there was no secondary rise. A similar delay was noted in a jaundiced dog with biliary obstruction but not in another with hepatitis.

Human Experiments: Serum estrogen was determined at 1, 5 and 24 hours in 10 patients after intramuscular injection of 240,000 i.u. of estradiol benzoate in oil. In two normal females and one male there were 116–180 i.u. per 100 cc. at 1 hour, at 5 hours the values were lower and at 24 hours only traces were demonstrable. Similar curves were obtained in a castrated woman and a woman with chronic nephritis. Delayed clearance was noted in 2 patients with hepatitis and 3 patients with cirrhosis of the liver.

The effects of mecholyl iontophoresis and of reflex thermal dilatation on the cutaneous blood flow. WALTER C. RANDALL and ALRICK B. HERTZMAN. *Dept. of Physiology, St. Louis Univ. School of Medicine, St. Louis, Mo.* The effects of mecholyl iontophoresis and of body heating on the cutaneous blood flow of the forearm and leg were measured by photoelectric plethysmographs. Resting blood flows averaged 0.032 cc/cm²/min in the forearm skin and 0.022 cc in the leg. Heat to the trunk resulted in profuse sweating and increased the flow 2.5 times in forearm skin and 3.5 times in leg skin. Cooling of the skin by evaporation probably prevented a maximal dilatation. Mecholyl iontophoresis increased the flow 5 times in forearm skin and 6.5 times in leg skin. The greater dilatation with mecholyl probably represents the maximal blood flow which can be provided in the skin at normal levels of blood pressure and therefore the maximum expansion of the cutaneous vascular bed. If a corresponding dilatation occurred over the entire skin surface of the body, it would deviate 1.5 liters/M²/min or 70% of the basal cardiac output to the skin. This is of the same order of magnitude as calculated from heat elimination in extreme exercise. The smaller values observed in the heat experiment raise the question: is so-called reflex thermal dilatation entirely due to decreased vasomotor tone or importantly due as well to the direct effects of temperature on the vessels? [*Aided by American Medical Association.*]

Effect of digitalis and strophanthin on the denervated lymph heart of the bullfrog (Rana catesbeiana). MARION A. REID. *Dept. of Physiology, Boston Univ. School of Medicine, Boston, Mass.* Denervated or transplanted lymphatic hearts develop cardiac-like properties which are in sharp contrast to those of the normal organ under neurogenic control (J. Exp. Zool., **76:** 47, 1937). Injections were made into the femoral vein. Simultaneous records of both anterior lymph hearts, 8 to 16 days after denervation of one of them, were obtained in bullfrogs anesthetized with urethane.

Doses of strophanthin (Kombé, Merck) or digitalis (usually 1–10 dilutions of the tincture) not exceeding the M.L.D. did not alter the rate of the control (innervated) lymph heart.

Injections of strophanthin, 12 to 39 per cent of the M.L.D. caused a three or four-fold acceleration of the denervated lymph heart. The typical periodic rhythm always became continuous in about an hour after the injections. The full M.L.D. increased the rate to 4.5 times that of the initial control within five minutes.

Similarly, injections of digitalis solutions (in amounts less than one-tenth frog unit) produced characteristically a continuous rapid rate in the denervated lymph heart, 1.7 to 2.8 times that of the control anterior organ. In one case the beating did not become continuous, but the duration of each spontaneous periodic series of beats increased from 7 to 27 minutes. Since the rate of such periodic lymph hearts was often rapid, the change to continous activity was the more striking effect of digitalis.

The denervated (myogenic) lymph heart is

stimulated by strophanthin or digitalis in a manner similar to their action upon isolated cardiac tissue. [*Aided by a grant from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association.*]

Maintenance requirement of desoxycorticosterone acetate of the adrenalectomized mouse and rabbit. H. REINHART (by invitation), A. CANTAROW, A. E. RAKOFF (by invitation) and K. E. PASCHKIS. *Jefferson Medical College and Hospital, Philadelphia.* While desoxycorticosterone and its esters are not capable of substituting entirely for adrenal cortical function, this compound is the most potent in producing sodium, chloride and water retention and is capable of maintaining life of the adrenalectomized animal as well as of patients with Addison's disease.

The amount of desoxycorticosterone acetate (D.C.A.) required for adequate maintenance appears to differ in different species.

Experiments were performed on 150 male white mice weighing about 20 Gm. in order to determine the maintenance dose of D.C.A. in this species. Adequacy of maintenance of the adrenalectomized mice was evaluated by (a) survival, (b) weight increase, and (c) resistance to potassium poisoning. D.C.A. was administered subcutaneously in oil solution at various dose levels, the volume of the vehicle being kept constant at 0.05 cc. per injection. Adrenalectomized controls received the same amount of oil without hormone. It was found that 0.5 mg. per day per mouse (weight 20 Gm.) or 2.5 mg. per Kgm. mouse per day was necessary for adequate maintenance. There was no significant difference in groups receiving tap water and those receiving 0.85% NaCl solution as drinking solution.

Preliminary experiments on rabbits showed that this species also has a high requirement. Daily injection of 2.5 mg. D.C.A. reduced the excessive chloride excretion of adrenalectomized rabbits weighing about 2 Kgm., but this dosage could not prevent weight loss. In spite of continued treatment, animals developed hemoconcentration and hypoglycemia and died in convulsions.

Analgesic and anticonvulsive properties of 3,5,5-trimethyloxalidine-2,4-dione (tridione). R. K. RICHARDS and G. M. EVERETT (by invitation). *Dept. of Pharmacology, Abbott Lab., North Chicago.* This compound was prepared by Dr. M. A. Spielman and is a white crystalline powder, soluble in water to 5 per cent. Addition of urethane or 10 per cent alcohol greatly enhances its solubility. Toxicity is quite low. The approximate L.D. 50 for rats subcutaneously is 2 gm./kg., for mice orally 2.2 gm./kg. and for rabbits intravenously 1.5 gm./kg. A hypnotic effect is present only with the higher dose levels. Acutely fatal doses cause respiratory and circulatory failure. With just lethal doses, the animals die in a state of coma several hours after administration.

The presence of a marked analgesic action was shown using different methods in mice, rats, and dogs. Also a marked antagonistic effect against the convulsive action of metrazol and picrotoxin could be demonstrated, but not against strychnine convulsions. Both the anti-convulsive and the analgesic effects in rats and mice were present with the non-hypnotic dose of 500–600 mg./per kg. of Tridione given parenterally.

If injected intravenously a dose of 25 mg./kg. produced a transitory fall of blood pressure in dogs and cats but the respiration remained practically unaffected. Preliminary clinical investigations have shown that Tridione is an effective analgesic both by oral and parenteral administration. Present evidence indicates that it surpasses the common coal tar analgesics in potency, particularly in visceral and postoperative pain.

Effects of intravenous injections of an aminoacid mixture on duodenal motility of anesthetized dogs. H. W. ROBINSON (by invitation) and M. J. OPPENHEIMER. *Depts. of Pediatrics and Physiology, Temple Univ. School of Medicine, Philadelphia, Pa.* Effects of intravenous casein digest upon duodenal motility were studied in dogs (Pentothal Na 15 mgm./kgm. Barbital Na 200 mgm./kgm.) by balloon methods. Arterial blood samples were taken under oil for CO_2 content and pH of serum, simultaneously a second sample was oxalated for determination of plasma aminoacid nitrogen; both two minutes before start of injection of casein digest. Another group of samples was drawn two minutes after injection ended. CO_2 content was measured with the Van Slyke-Neill manometric gas apparatus. pH was determined at 38° by the glass electrode in a cell which provided minimal exposure to the sample to atmosphere. Aminoacid nitrogen was measured by the gasometric-ninhydrin procedure.

Infusions of 6.5 cc. Mead Johnson Amigen/kgm. produced hypermotility of short duration. This occurred during or within a few minutes after end of injection. Under these conditions aminoacid nitrogen values rose from averages of 3.8 to 25.0 mgm/100 cc. plasma. Amigen (pH 5) never lowered serum pH more than 0.07 nor CO_2 more than 10 volumes per cent.

Similar results were obtained in other experiments when a slow intravenous drip of 5 per cent $NaHCO_3$ was used to prevent the acid shift caused by Amigen. This increased tonus and amplitude was also present when the aminoacid mixture was given to animals rendered acidotic (pH 7.02) or to others alkalinized (pH 7.50). In a few cases hypermotility due to Amigen was followed by a longer period of inhibition. [*Aided by a grant from Mead Johnson and Company.*]

Acetylcholine and the response of the crayfish nerve cord to low external potassium. K. D. ROEDER. *Dept. of Biology, Tufts College, Mass.* Previous studied by Prosser (J. Cell. and Comp. Physiol. **15:** 55, 1940, **22:** 131, 1943) and Roeder (ibid. **18:** 1, 1941) show that a reduction of the external potassium may either increase or decrease the intrinsic nervous activity of the isolated ventral nerve cord of the crayfish. Typically, reduced K is excitatory while the cord is *in situ* and for the first hour or two in saline. After 2–3 hours isolation reduced K reversably depresses the intrinsic activity, and continues to have this effect until the cord becomes inactive (about 30 hours). In a small percentage of cords low K is excitatory throughout the life of the preparation, though these cords appear to be normal in other respects.

The reversal of the response to low K implies some progressive internal change as the preparation ages. This change does not always occur and is unrelated to activity level or time of survival.

If the stage has been reached when low K is depressant and the cord is bathed in saline containing acetylcholine 10^{-4}, a subsequent reduction in K increases activity as in a fresh preparation. This effect may be obtained repeatedly until the acetylcholine is replaced by saline, when low K becomes once more depressant after about 30 minutes. Smith (J. Cell. and Comp. Physiol. **13:** 335, 1939) has shown that crayfish blood contains acetylcoholine 10^{-6} which accounts for the potassium response of fresh cords. The reversal of the low K response in the majority of cords in saline must result from the progressive loss of intrinsic acetylcholine through diffusion or cholinesterase action.

Palmer skin resistance (P.S.R.) during a standard period of controlled muscular activity as a measure of physical fitness. A. H. RYAN and E. L. RANSEEN (by invitation). *Lab. of senior author and Research Lab. Quaker Oats Co., Chicago, Ill.* Subjects mounted a bicycle ergometer and placed their entire palms in shallow pans containing a one per cent solution of sodium chloride maintained at body temperature. P.S.R. measured by a simple bridge at 45 or 55 seconds during a one minute period of work at constant speed and load appears to be related to physical fitness. P.S.R. during work has been described (Am. J. Physiol. **133:** P434, 1941).

Heavy muscular work followed by inadequate time for recovery resulted in marked increases of P.S.R. in the standard work period.

In daily experiments on 15 subjects during a period of 4 weeks a very significant positive correlation was found between variability of sleep and variability of P.S.R. Large sleep losses incurred by some of these subjects and experimentally induced in other subjects resulted in marked increases in P.S.R. from which recovery with normal sleep was not immediate.

For the 15 subjects day to day changes of P.S.R. gave a negative correlation with day to day changes of total work performed on the ergometer in five consecutive one minute work periods with half minute rest pauses. The load was such that the speed could not be maintained in the later work periods. A Pearson r of $-.33$ was obtained with a Fisher t of 5.6.

The theoretical basis for these results appears founded on the relation of sweat gland activity measured as P.S.R. to sympathetic activity, and the relation of sympathetic activity to physiological stresses.

Do stomachs of patients with duodenal ulcer manifest a hypercontinuous nocturnal gastric secretion? D. J. SANDWEISS (by invitation), H. M. PODOLSKY (by invitation), A. D. RUSH (by invitation) and T. L. PATTERSON. *Dept. of Internal Medicine, Harper Hospital and Dept. of Physiology, Wayne Univ., College of Medicine, Detroit, Mich.* Previous studies have shown that after a 6 P.M. meal the gastric juice aspirated hourly from duodenal ulcer patients (8 P.M. to 8 A.M.) was approximately of the same concentration of free hydrochloric acid as was the juice collected from normal subjects (Sandweiss et al. "Nocturnal Gastric Secretion Studies on Normal Subjects and Patients with Duodenal Ulcer," North End Clinic Quart., **4:** 4, 1943). However, the total amounts aspirated during the night (totalling the amounts aspirated once hourly) was approximately twice as much for the ulcer patients. This raised the question whether it was due to a state of hypersecretion or delayed emptying.

Over 50 additional nocturnal gastric secretion studies were performed on 15 normal male subjects and 15 male duodenal ulcer patients, with the exception, that after the stomach was completely emptied at midnight, the Levine tube was attached to a continuous suction apparatus. The stomach was thus continuously aspirated throughout a seven hour period from 12 midnight to 7 A.M. (instead of one aspiration hourly as was done in the previous study). It was felt that continuous aspiration would to a great extent exclude the factor of "delayed emptying."

Appreciable variations occurred, but on the average, approximately 400 cc. of juice was aspirated from the stomachs of duodenal ulcer patients and approximately the same amount was obtained from the stomachs of the normal subjects, indicating that our ulcer patients did not manifest a state of hypersecretion (there was one exception) but rather, a state of delayed emptying.

Influence of morphine, alcohol and sulfanilamide on respiratory discharges. W. A. SELLE. *Dept. of Physiology, Medical School, Univ. of Texas, Galves-*

ton. Using unperfused isolated heads of 12–15 day-old rats as test preparations and a technique previously described, it is found that a number of drugs alter the activity of the respiratory center under anaerobic conditions. As indicated by the gasping pattern, activity of the center of control animals is uniform and continues for slightly more than 4 minutes after isolation of the head. This pattern consists of: (1) an initial series of 8–10 aerobic gasps within a period of 15–20 seconds, (2) an interseries interval of 30.45 seconds, (3) an anaerobic series of 18–24 rhythmic gasps lasting about 240 seconds.

Unless given in obviously toxic doses, the drugs tested have little effect on the aerobic series. Morphine sulphate (.2–.8 mg.) injected subcutaneously ½–1 hour prior to isolation of the head increases the survival period by 150% and the total number of gasps of the second series by 200%; the interseries interval tends to decrease. Ethyl alcohol gives similar results; however, the duration of survival is less prolonged than in cases of morphine and the total number of gasps is greater. Sulfanilamide (2–6 mgm.) also produces similar but less marked changes. One feature common to these drugs when given in large doses is the formation of accessory gasps between normally occurring ones. Although rhythmic, they are similar and more frequent than the normal or dominant ones and out of phase with them. They frequently show a progressive increase in amplitude for short periods, the pattern usually being repeated. Such accessory gasps appear to be due to ectopic "pace makers" or to recirculation of excitatory waves over one or more pathways by a process analogous to that involved in the circus movements of the heart.

Dilating substances in mold extracts used in skin testing. W. A. Selle and Hommer Prince (by invitation). *Dept. of Physiology, Univ. of Texas, Medical School, Galveston.* Extracts of certain molds used extensively in skin testing of allergic individuals produce marked reactions in normal subjects injected intracutaneously with relatively high dilutions. Since histamine can be isolated from certain fungi (e.g., Claviceps purpurea), it was suggested that this capillary dilator might be responsible for the non-specific reactions of the mold preparations.

Two clinically important fungi, Alternaria and Aspergillus, both widely distributed and frequently occurring, were selected for study. Although allergenically important, both molds rank high among those frequently producing non-specific reactions. The fungi were grown on a standard malt-extract broth. When the pellicles reached maturity they were harvested, washed with several changes of 0.9 per cent saline, frozen and dried. Extracts of the dried material were prepared by five different extraction methods. Each extract was assayed for histamine by physiological methods employing the technique of Schultz and Dale. Using target tissues (ileum and uterus of young guinea pigs) known to be sensitive to histamine in dilutions of 1:300,000,000, positive responses could not be obtained with any of the extracts. Since the histamine sensitivity of the test preparations was roughly 1,000 times that of normal human skin, it is assumed that this amine is not the irritating agent in the mold extracts. Other possible irritants are being studied.

Prevention of experimental nephrosclerosis with methyl-testosterone. Hans Selye and E. M. Rowley (by invitation). *Department of Anatomy, McGill Univ., Montreal, Canada.* Experiments on female albino rats having an average weight of 60 g. have shown that the nephrosclerosis and proteinuria elicited by five weeks subcutaneous treatment with 4 mg. of desoxycorticosterone acetate (D.C.A.) per day, can be almost completely counteracted by the simultaneous daily subcutaneous administration of 10 mg. of methyl-testosterone.

This experiment was repeated under identical conditions in rats sensitized to the nephrosclerotic action of D.C.A. by unilateral nephrectomy. In this series the nephrosclerosis inhibiting action of methyl-testosterone was equally obvious.

These experiments confirm our view that the nephrosclerotic and renotropic actions of steroids are independent of each other and indeed actually antagonistic. The strong testoid or "androgenic" effect of methyl-testosterone counterindicates its clinical use especially in female patients suffering from nephrosclerosis, but preliminary experiments suggest that other steroids have a more favorable testoid:renotropic ratio.

In view of the frequent association of changes in blood cholesterol and renal disease in men, we wish to mention that in our experiments D.C.A. caused a statistically significant hypercholesterolemia in the nephrectomized group and that this effect was actually reversed by simultaneous methyl-testosterone treatment.

The effect of external constriction of a vessel upon blood flow. R. E. Shipley (by invitation) and D. E. Gregg. *Dept. of Medicine, Western Reserve Univ., Cleveland, Ohio.* The effect of an external constriction of a blood vessel in limiting blood flow has been considered with respect to the relationships of 1) vessel bore to volume flow and 2) change in external to change in internal dimensions of the vessel. Experiments with an artificial system and in animals have led to the conclusions that:

The effect of a localized reduction in lumen area is primarily that of increasing the fluid friction (viscosity effect) at the site of the construction, which results in an added "peripheral resistance"

to the flow of blood and the rate of flow is thereby reduced.

The extent of flow reduction will vary in direct relation to the axial length of the constricted area, the velocity of flow and the viscosity of the blood, and in inverse relation to the peripheral resistance of the bed and the lumen area of the vessel constriction. Since, with an intact blood vessel, it is impossible to determine all of the above factors, an estimation of the flow reduction caused by a given constriction will be only as accurate as the estimated values placed upon the determining factors. Without the observer's knowledge, marked changes in the determining factors may occur, thereby making it impossible to predict within rather wide limits either the immediate or subsequent effects of a known constriction.

The experimental findings reveal no justification for the contention that a rather marked degree of external constriction is required to produce a significant reduction in flow through a vessel. [*Supported by a grant from the Commonwealth Fund.*]

Influence of progressive dehydration on the polyuric response of white rats exposed to low barometric pressure. HERBERT SILVETTE. *Dept. of Pharmacology, Univ. of Virginia, Charlottesville.* Normal white rats allowed water ad libitum excreted about 300 per cent more urine when exposed for 3 hours to a barometric pressure of 282 mm. Hg (25,000 ft. altitude equivalent) than control rats at 760 mm. Hg (Amer. J. Physiol., **140:** 374, 1943). In order to determine whether this polyuria would still develop in the presence of progressively severe dehydration, a series of animals was deprived of water, or of both food and water, for periods of 24, 48, and 72 hours, allowing sufficient time between experiments for the animals to regain their original weight. At the end of each period of water deprivation, the animals were exposed to a pressure of 282 mm. Hg for 3 hours, and their urine collected. The following table gives the results obtained (averages of 24 animals):

Barometric pressure (mm. Hg)	3-hr. urine output cc./100 gm. after withholding water for			
	0 hrs.	24 hrs.	48 hrs.	72 hrs.
760	0.4	0.2	0.2	0.1
282	1.6	0.4	0.2	0.1

No difference was observed in the response of dipsotic, or of both fasted and dipsotic, animals to exposure to low pressures.

The experiments indicate that the high-altitude polyuria occurs only in the presence of an adequate supply of body water. When the body-water content was decreased, by means of water deprivation for periods longer than 24 hours, the necessity of the kidneys to conserve body water overbalanced the diuretic action of high-altitude exposure. [*This investigation has been made with the assistance of a grant from the Ella Sachs Plotz Foundation.*]

The effect of hemorrhage and transfusion on the ability of the rabbit to withstand reduced atmospheric pressure. EDWIN L. SMITH (introduced by E. Fischer). *Dept. of Physiology, Medical College of Virginia, Richmond.* Three groups of rabbits were subjected to progressively decreasing atmospheric pressure. The rate of decrease was such as to stimulate as ascent of 1000 feet per minute, and was continued until death as evidenced by cessation of respiration. Group 1 consisted of 6 normal rabbits. Group 2 consisted of 6 rabbits that had been bled, by puncture of the femoral artery, to an amount approximating 1% of body weight. Group 3 consisted of 6 rabbits that had been injected intravenously with heparinized whole rabbit blood in an amount approximating 1% of the body weight. Groups 2 and 3 were allowed 3 to 4 hours following the experimental procedure before decompression was started. All experiments were carried out at a rather high (26°–30° C.) room temperature.

No significant difference was present between any of the groups. The average height attained by group 1 (control) was 28,666 ft. with extremes of 30,000 ft. and 27,000 ft.; of group 2 (bled) was 29,166 ft. with extremes of 31,000 ft. and 26,000 ft.; of group 3 (transfused) was 28,666 ft. with extremes of 31,000 ft. and 27,000 ft.

The results of ablation of the cingular region of the cerebral cortex. WILBUR K. SMITH. *Dept. of Anatomy, The Univ. of Rochester School of Medicine and Dentistry, Rochester, N. Y.* In monkeys (Macaca mulatta) bilateral ablation of the rostral part of the cingular gyrus (mostly area 24 of Brodmann) results in temporary but definite alterations of functions. Subsequent or simultaneous removal of the caudal part of the cingular region does not seem to alter the results. For several days after the operation the animals appear stuporous, and there is a marked decrease in activity, the animal sitting for long periods of time with the head bent low. Often the head sinks down slowly and is then suddenly raised only to sink down again. Vocalization is increased in frequency, occurring apparently spontaneously, as well as on the slightest provocation. Contraction of the arrectores pilorum muscles causes a "goose flesh" appearance of the skin and also piloerection which is most pronounced over the upper part of the trunk and the upper extremities. Blowing on the erect hair causes a vigorous startle reaction as if there is an increased cutaneous sensibility to this type of stimulus. The animals appear less frightened when approached and, instead of running away and crouching in the far corner of

the cage, will now take food from one's hand. However, they will not permit themselves to be handled. The decreased activity and the excessive vocalization disappear in about a week, but the piloerection and the "tameness" persist for many weeks. The results of these experiments are not in agreement with the findings of Horsley and Schafer (1888) who reported that ablation of the cingular gyrus resulted in a contralateral hemianesthesia. [*Aided by a grant from the John and Mary R. Markle Foundation.*]

The results of stimulation of the uncus and adjacent portions of the hippocampal gyrus. WILBUR K. SMITH. *Dept. of Anatomy, The Univ. of Rochester School of Medicine and Dentistry, Rochester, N. Y.* The functional significance of the hippocampal gyrus and its hook-like termination the uncus is unknown. The fact that it has developed phylogenetically and embryologically in close association with the hippocampus and the basal olfactory cortex of the brain has caused some investigators to assign it to the rhinencephalon, thus imputing to it an olfactory function. However, the presence of a well developed hippocampal gyrus in the brain of the dolphin (Broca, 1878) and in that of the porpoise (Langworthy, 1932), both of which lack olfactory nerves, bulb and tract, is strong evidence in favor of the view that the hippocampal gyrus is concerned with functions other than, or in addition to, olfaction.

In experiments on monkeys (Macaca mulatta), it has been found that electrical stimulation of the uncus and the adjacent part of the hippocampal gyrus produces vocalized responses similar to those which the animal ordinarily emits. A characteristic feature of the response is its prolongation beyond the period of stimulation. In addition to vocalization, excitation of this region produces a marked decrease in the heart rate, accompanied by increased pulse pressure. In this instance also the effect outlasts the stimulation. The administration of eserine in adequate amount results in marked accentuation and prolongation of the cardiac inhibition resulting from the cortical excitation. That the cardiac inhibition is produced by impulses passing over the vagi is indicated by the similarity of the response to that obtained by excitation of the vagus nerve, and seems proven by the abolition of the response after section of the vagi. [*Aided by a grant from the John and Mary R. Markle Foundation.*]

A method of producing an artificial jaundice. F. E. SNAPP (by invitation), TSAN-WEN LI (by invitation), J. E. HABEGGER (by invitation) and A. C. IVY. *Dept. of Physiology, Northwestern Univ. Medical School, Chicago, Ill.* When a water solution of the sodium salt of bilirubin was injected intravenously in an attempt to produce jaundice in dogs the bilirubinemia gave only the indirect van den Bergh reaction. The sodium salt of bilirubin added to blood plasma in vitro also gave an indirect reaction. When a certain excess of alkali was added to bilirubin in plasma a direct reaction resulted. When this plasma-bilirubin mixture was injected intravenously into dogs a direct-reacting bilirubinemia resulted. By a series of five injections of 50 mgm. of bilirubin each over a 4–6 hour period in ten experiments on 6 dogs we produced a jaundice in the dogs. Varying peak blood levels of bilirubin were obtained from 14–18 mgm. per cent. The level dropped rapidly during the first few hours and afterward fell gradually to about 0.5 mgm. per cent after a week.

Three dogs were given a series of injections of bilirubin-plasma mixture every 3 or 4 days for three weeks. A considerable blood level of bilirubin was maintained and a marked icterus of the sclera lasted during the injection period and for several weeks afterward.

The dogs receiving a single series of injections and those receiving repeated injections over longer periods did not manifest any permanent damage of the liver as measured by Rose Bengel Clearance and blood serum phosphatase levels. [*This study was assisted by a grant from G. D. Searle & Co.*]

Experimental asphyxia neonatorum. FRANKLIN F. SNYDER. *Depts. of Anatomy and Obstetrics, Harvard Univ.* In observations on the mechanism of the tolerance to anoxia of the fetus at birth, the time of survival of newly born rabbits was determined following asphyxia by various methods including ligation of the trachea. Tracheal ligation is a simple method for studying asphyxia under conditions simulating closely the accidental impairment of the umbilical cord circulation in the course of birth. Instead of elimination of CO_2 in the period of hyperpnea associated with the onset of the breathing of nitrogen, no exchange is possible, just as is the case when the fetus is in the birth canal. Whether or not the accumulation of CO_2 in the body under such circumstances is an added source of injury to the fetus has been debated frequently. Especially in connection with the rationale of resuscitation of apneic infants the question has been unsettled as to whether or not pure oxygen should be used rather than a mixture of 5% CO_2 and oxygen. In the present observations kymograph tracings of the respiratory movements were obtained in 85 newborn rabbits from 45 litters which were selected at various stages from the time of onset of viability until the end of lactation. Results showed that there was no decrease in the time of survival following tracheal ligation as compared with survival time in nitrogen. In fact, following tracheal obstruction, respiratory movements continued for a longer period usually than in animals asphyxiated in nitrogen.

The effect of ions on the frog vascular system. C. R. SPEALMAN. *Dept. of Physiology, Medical College of Virginia, Richmond.* In previous experiments concerning the effects of ions on the perfused heart, it was found that when the concentration of any of the cations of Ringer's solution was outside its own characteristic concentration range, certain non-specific depressant effects occurred. On the basis of these findings the concept of "normal concentration limits" was formulated and these limits were roughly defined.

The present experiments represent an attempt to extend this concept to the perfused blood vessels of the frog. Three different perfusion preparations were used: the whole frog, the hind legs, and the systemic arches. The perfusion fluid came from a Marriotte flask whose air inlet tube was so arranged as to give pulsatile pressure. The procedure was to perfuse with control Ringer's solution for one-half hour, then with the experimental Ringer's solution until a definite change occurred or until it was certain that no effect was to be expected, and finally with normal Ringer's solution again.

Preliminary results indicate that the perfusion rate is decreased (vasoconstriction) when the concentration of any of the cations (Na^+, K^+, Ca^{++}, H^+) is too high or too low. The concentration limits of the various cations for this effect appear to be similar to the "normal concentration limits" established for the perfused frog heart with some exceptions, e.g., the lower concentration limits for Ca^{++} and K^+ seem to be lower for the blood vessels than they are for the frog heart.

Depressor effect of cold upon the static receptors of the labyrinth. E. A. SPIEGEL. *Dept. of Exp. Neurology, Temple Univ. School of Medicine, Phila., Pa.* A u-shaped cannula introduced into the external and middle ear of decerebrate cats was perfused with water of from 3°–20°C. Water of 9° or below produced within a few minutes a decrease in the muscle tone of the homolateral foreleg, causing a drooping of this leg, in some instances also the opposite foreleg showed a similar effect. This effect may outlast the calorization, but is reversible. Similar, although less pronounced, effects were observed in rabbits with intact brain, in supine position. The effect of unilateral cooling upon the posture of the head was demonstrated in unanesthetized rabbits and in cats under bulbocapnine catalepsy by keeping the perfused cannula for several minutes in the external and middle ear and then quickly withdrawing it so that its weight did not influence the posture. The cold temporarily produced effects similar to those of unilateral labyrinthparalysis: a rotation of the head about the oro-occipital axis, the affected ear lying lower. The excitability of the cristae revealed no significant difference of the postrotatory nystagmus in cats rotated before, and during, prolonged application of cold to both ears. Thus a depressor effect of cold could be observed only on static receptors influencing the posture of head and extremities (apparently chiefly the maculae), while such an effect upon the receptors reacting to angular acceleration was not noticeable. [*The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Temple Univ.*]

The receptor mechanism of vestibulo-vasomotor reactions induced by rotation. E. A. SPIEGEL, M. J. OPPENHEIMER and H. T. WYCIS (by invitation). *Depts. of Exp. Neurology and of Physiology, Temple Univ. School of Medicine, Philadelphia, Pa.* Two groups of experiments were performed. In the first series the round windows were bilaterally punctured in cats. Following this operation, rotation failed to produce rhythmic ocular movements, while a reflex depression of the blood pressure could still be elicited by rotation of the body around a longitudinal or around a dorsoventral axis. Subsequent injection of a 2% alcoholic cocain solution into both labyrinths transitorily abolished the vasomotor reaction, indicating in agreement with previous extirpation experiments of one of the authors, that the receptor apparatus lies in the labyrinth. In a second group of experiments guinea pigs were subjected to centrifugation (method of Wittmaak; Magnus- de Kleyn). Following this procedure the animals were tested during the stage in which the tonic labyrinthine reactions were paralyzed. In this stage rotation was still able to produce a fall in blood pressure. Thus, paralysis of the receptors for labyrinthine kinetic reactions such as the rhythmic eye jerks, or of the receptors for tonic labyrinthine reflexes does not prevent the vasomotor reaction to rotation while cocain paralysis of the labyrinth abolishes this reaction. These experiments seem to indicate that this vasomotor reaction originates in receptors for kinetic as well as in receptors for tonic reactions. [*The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Temple Univ.*]

Effects of electrically induced convulsions upon the brain revealed in the cerebrospinal fluid. M. SPIEGEL-ADOLF (by invitation), E. W. ASHKENAZ (by invitation), A. J. LEE (by invitation) and E. A. SPIEGEL. *Depts. of Exp. Neurology and of Colloid Chemistry, Temple Univ. Medical School, Philadelphia, Pa.* Epileptiform convulsions were induced in 25 dogs by alternating currents, the electrodes being placed in the conjunctival sacs. Before and after a series consisting of 1–15 convulsions, conductivity, total interferometric value (TIV) of the cerebrospinal fluid (CSF), P and K

content of serum and CSF were determined (table), and in some animals the permeability of the blood-liquor barrier was estimated by the uranine method. The ratio of interferometric value of the non-electrolytes (INE) to that of the electrolytes (IE) was calculated from the conductivity and TIV. The following mean values were obtained:

	Conductivity	TIV	$\frac{INE}{IE}$	P (mg. %)	K (mg. %)	$\frac{P\ ser}{CSF}$	$\frac{K\ ser}{CSF}$
Before convulsions	1.39×10^2	514	0.596	1.72	12.49	3.4	1.59
After convulsions	1.41×10^2	527	0.632	1.96	14.63	3.05	1.61
Significance of difference (probability integral)	0.037	<0.01	<0.01	<0.02	<0.01	0.3	0.13

A statistical computation of the data showed that, following the convulsions, the total amounts of electrolytes (indicated by the conductivity), $\frac{INE}{IE}$, K and P content of the CSF were significantly increased, while the permeability of the blood-liquor barrier for K and P ratio $\left(\frac{ser.}{CFS}\right)$ was not significantly altered. Nor could changes of permeability of the blood-liquor barrier, as a result of convulsions, be found by the uranin method, in comparison with controls without convulsions.

A theoretical study on the effect of aortic size on the ballistocardiogram. ISAAC STARR. *Research Dept. of Therapeutics, Univ. of Penna., Phila.* Consider an aorta of cross-section c divided into a series of n segments, the volume m of each equaling the cardiac stroke volume. The average systolic velocity in the aorta $= v$ and $\frac{dv}{dt} = a$. Then the impact from each segment $= ma$, the total impact $= [m_1a + m_2a + \cdots m_na]$. Now consider the effect of doubling the aortic cross section without altering stroke volume. Then the aortic velocity becomes $\frac{v}{2}$, the acceleration $\frac{a}{2}$, the impact of each segment $= \frac{ma}{2}$. This was visualized in our cardiac output formulae (Am. J. Physiol. **127**: 1, 1939) and was the basis of the supposed need for estimating aortic size.

But this conception neglects the fact that the enlarged aorta contains twice as much blood, and $2n$ segments. The sum of their impacts

$$\left[\frac{m_1 a}{2} + \frac{m_2 a}{2} + \cdots \frac{m_{2n} a}{2}\right] = [m_1 a + m_2 a + \cdots m_n a].$$

Any change in aortic diameter changes velocity and volume inversely; the effect on impact cancels out.

This reasoning suggests that our cardiac output method would be improved by abandoning the attempt to estimate aortic size in each subject and employing a constant instead. It suggests that we have been overestimating the circulation in elderly persons relative to young ones, and to a less extent in large as opposed to small persons. The latter explains our finding that the average cardiac output of women was a little smaller than that of men (J. Clin. Invest. **19**: 437, 1940). But the new conception gives promise of removing a step subject to grave error from our procedure.

The effects of acetyl-beta-methylcholine in human subjects with localised lesions of the central nervous system. G. W. STAVRAKY and S. M. FISHER (by invitation). *Dept. of Physiology, Univ. of Western Ontario Medical School and Westminster Hospital, London, Canada.* In 11 male human subjects with lesions of the frontal lobe, with and without involvement of the pyramidal system, intramuscular injections of 8–10 mgm. of Mecholyl (Merck) administered with the patients in a recumbent position produced an asymmetrical response. A widespread erythema was observed with some blanching. The blanching was particularly pronounced contralaterally, often involved whole extremities and was followed by a delayed flush after the ipsilateral erythema had subsided. During the reaction, which lasted 4–6 min. the contralateral extremities were colder than the ipsilateral ones; also there was an asymmetrical distribution of sweating. In the early stages of the response a delay in the sensation of heat on the opposite side of the face and a transient dilatation of the contralateral pupil were commonly noted. Occasionally the pupil became irregular in outline and did not constrict as readily to light as the ipsilateral one. Muscular tremors, hyperreflexia, an increase of spasticity, wrist and ankle clonus and prominence of pathological reflexes on the opposite side of the body characterised the later stages of the reaction.

It was shown in animals (Stavraky, G. W., Trans. Roy. Soc. Canada, vol. 37, sect. 5, p. 127, 1943) that, in accordance with Cannon's "Law of Denervation" a permanent sensitisation to acetylcholine takes place in neurones which were directly connected with surgically removed parts of the brain. A similar sensitisation of certain regions of the nervous system to acetyl-beta-methylcholine in human subjects can account for the present results.

The effects of conditions similar to high altitudes on colon size in dogs. F. R. STEGGERDA and A. B. TAYLOR (by invitation). *Dept. of Physiology, Univ. of Illinois, Urbana.* Dogs with co-

lons previously made permanently opaque to x-rays with thorium dioxide (Thoratrast) were subjected to negative pressures corresponding to altitudes of 15,000 to 35,000 feet for varying periods of time (5 to 60 minutes). In experiments lasting more than 30 minutes, oxygen was supplied. The dogs were starved for 25 hours previous to the time of the experiment so that the colon might be free of fecal material. X-ray pictures of colon size at various altitudes were taken and the area measured by means of the planimeter. Twenty-four different experiments were performed using ten dogs. In all cases Nembutal anesthesia was used.

An examination of the data obtained shows that colon size is not altered appreciably up to altitudes of 20,000 feet, whereas above this level a progressive increase in size was observed in most cases. In four cases no ballooning was observed at high altitudes, but when known quantities of gas were injected into the colon by way of the rectum, a marked distention occurred at high altitudes.

Further examination of the data shows that there is a tendency for the colon size to decrease with time after the desired altitude is reached and maintained. Evidence that this is not due to the absorption of the gas by way of the mucosa, but rather due to excretion by way of the rectum is reported elsewhere. Peristaltic activity was observed to be more marked below 27,000 feet than above.

The recovery of the cut surface of the scallop muscle. H. B. STEINBACH and N. KAWATA (by invitation). *Dept. of Zoology, Washington Univ., St. Louis.* The rate at which a cut surface of the scallop muscle changed to restore the normal membrane conditions as indicated by the injury potential was measured by methods already outlined in general (Steinbach, Jour. Cell. and Comp. Physiol., vol. 3, p. 203, 1933). Since the initial change is nearly linear with time, the time in minutes for the first 10 millivolts change is used as a convenient experssion of rate. In normal sea water, the 10 millivolts time ranged from 10 to 14 minutes.

Confirming earlier studies, excess calcium in sea water increases the rate (2–3 min.). Other agents causing comparable increases in rate upon prolonged soaking of the muscles were iodoacetic acid (6.5 min. at 0.001 M, 3 min. at 0.04 M), and intermediate concentrations of phenyl urethane (4–7 min. ¼ saturated solution). Ca-free solutions, calcium precipitants (oxalate and fluoride) and saturated phenyl urethane caused marked decreases in rate (50 min. or longer) also decreasing though not, as a rule stopping the effects of subsequently applied calcium or iodoacetate.

The effects of the agents are consistent with the known phenomena of membrane repair (see Heilbrunn, *Outline of General Physiology*) except those of iodoacetate. Concentrations of iodoacetate were high enough presumably to inhibit both oxidation and glycolysis. Other agents that might be expected to act on enzyme systems through sulfhydryl groups (p-phenylene diamine, copper salts, ferricyanide) were without effects as were succinate and pyruvate. It is probable that the iodoacetate effect is specific on the membrane formation and not related to its usual metabolic effects.

Rectification and injury potential in squid axons. H. B. STEINBACH, S. SPIEGELMAN (by invitation) and N. KAWATA (by invitation). *Dept. of Zoology, Washington Univ., St. Louis.* The apparent resistance of the single giant axon to d.c. currents of short duration was measured by a simple wheatstone bridge device, electrodes being applied at an uninjured region and an injured end in isotonic KCl solution. The difference in resistance with current flow inwardly and outwardly directed was taken as a measure of rectification, presumably by the axon membrane. In accordance with findings of previous workers the resistance is lower when the cathode is at the uninjured region, the difference between the two orientations of electrodes depending on the current flow among other things.

Change in rectification and injury potential measured on the same preparations and nearly simultaneous were recorded as the ionic environment was altered. At low concentrations of potassium, changes in potassium content had little effect on rectification but caused a marked decrease in injury potential. Potassium in concentrations increased above that of normal sea water caused the decrease in injury potential reported in other studies and also caused a very drastic fall in rectification.

Calcium, in wide range of concentrations, had little effect on injury potential, but caused impressive increases in rectification frequently more than doubling the rectification at calcium concentrations two to three times that of normal sea water. Excess calcium also tended to prevent the drop in rectification due to excess potassium although having little effect on the decrease in injury potential. It seems reasonable that rectification should be a measure of membrane stability, probably better than the injury potential which is less sensitive to environmental changes.

Intestinal absorption during histotoxic anoxia. J. CLIFFORD STICKNEY (by invitation), DAVID W. NORTHUP and EDWARD J. VAN LIERE. *Dept. of Physiology, School of Medicine, West Virginia Univ., Morgantown.* The absorption (during 40 min.) of Cl, Na, SO; and fluid from 100 cc. of a solution of ½ isotonic NaCl and ½ isotonic Na_2SO_4 in Moreau loops (lower 45 to 60 cm. of the small intestine) in 20 fasting, paired, barbitalized dogs was determined. In the experimental animals KCN was injected by vein intermittently and symptomatically to produce during the absorption period

a marked decrease in the oxygen consumption which was measured in both experimental and control animals with a Sandborn basal metabolism apparatus. Carotid blood pressure was recorded directly throughout. Cl was determined by the Van Slyke modification of the Volhard method, Na by the Butler and Tuthill method and SO_4 gravimetrically.

The average reduction of oxygen consumption in the experimental dogs ranged from 13 to 48 per cent. In these dogs the KCN produced a marked depression of the blood pressure; this variable was uncontrolled.

The per cent absorption in control and experimental dogs respectively was 82 and 76 of the Cl, 52 and 53 of the Na, 27 and 30 of the SO_4 and 58 and 60 of the fluid. The final concentrations of Cl in the fluid in the loops of the control and experimental dogs were 30.9 and 42.4 m. eq./l. respectively, while those of the other ions were practically the same in both groups. Histotoxic anoxia produced no statistically significant differences under the conditions of the experiments.

Emotional effects of oral examinations upon blood pressure and pulse rate. G. A. TALBERT. *Dept. of Physiology, Univ. of North Dakota.* For the purpose of determining the emotional effects on blood pressure and pulse rate, tests were made on physiology medical students appearing for individual oral examinations lasting on an average of fifteen minutes.

There were selected 79 different male students, and in all, 323 experiments were performed. Determinations were made on the systolic and diastolic pressures immediately before and immediately after the examination, likewise the pulse rate. Comparisons were made with the normal. Any change of less than 3 mm. pressure was disregarded.

Before the examination there was a rise in 61 per cent of the cases and 62 per cent of the cases after the examination. Either before or after there was a rise in 80 per cent of the cases.

In the diastolic pressure there was a rise of 23 per cent of the cases either before or after. Quickening of the pulse rate was more manifest but with no apparent correlation with blood pressure. Attempt was made not to unduly excite the student as so commonly noted by a cross examiner in courts of law.

Studies of the activity of the dog's colon following the administration of gas. A. B. TAYLOR (by invitation) and F. R. STEGGERDA. *Dept. of Physiology, Univ. of Illinois, Urbana.* In these experiments dogs with colons made previously opaque to x-rays with thorium dioxide (Thoratrast) were used. Alterations in size of the colon were recorded on x-ray films, and the areas measured by means of the planimeter. The injection of the gas (room air) into the colon was done by cementing an improvised rubber funnel to the anus. By means of a burette and manometer attachment to the funnel, it was possible to record the amount of gas both administered and excreted by way of the rectum, as well as the motility and pressure alterations accompanying such changes. Nembutal anesthesia was used, and the observations were made on 5 dogs for 12 different experiments. In all cases the colon was empty before starting the experiment.

The results show that when 50 to 100 cc. of gas are administered there is an appreciable increase in colon size which remains this same size or even increases for a period of one to two hours, provided the gas is not allowed to escape by way of the rectum. Upon releasing the clip on the rubber funnel, we were able to collect an average of 85% of the gas administered. This gas was usually expelled in large quantities at first, but often continued to escape in smaller quantities for two to three hours. These observations indicate that under these conditions little or no gas is absorbed directly by way of the colon mucosa.

In experiments where pressure and motility changes were measured following the gas administration, there occurred variations in pressure from 4 to 35 cm. of water. The increase in pressure corresponded with marked contractions of the colon. In experiments in which an antispasmodic drug was administered intravenously, both motility and pressure were markedly reduced, and colon size was increased.

The quantitative relationship between the colloid osmotic pressure of blood plasma and the A/G ration. HENRY LONGSTREET TAYLOR (by invitation) and ANCEL KEYS. *Lab. of Physiological Hygiene, Univ. of Minnesota, Minneapolis.* The colloid osmotic pressure effects of the known important factors in blood plasma are covered in the following theoretical equation:

$$P = \frac{10\alpha_a \cdot C_a \cdot RT}{m_a} + \Delta\beta \frac{10\alpha_g \cdot C_g \cdot RT}{m_g}$$

where the subscripts a and g stand for albumin and globulin respectively; P is the colloid osmotic pressure in mm Hg; C is the protein concentration in grams per 100 cc. water; m is the molecular weight of the protein; α is an osmotic activity coefficient which includes the Donnan effect, hydration of the proteins, etc.; Δ is a dissociation factor for globulin in the presence of albumin at concentrations of 0 to 3.5 grams of total protein per 100 cc. water; β is an additional dissociation factor for globulin at higher concentrations of total protein; and R and T have their usual significance. Values for m and α were derived from separated solutions of albumin and globulin; Δ and β on various diluted plasmas, the point of reference being the

Na_2SO_4 A/G ratio. Thus Δ and β include the error inherent in this method. The equation can be put into the following usable form:

$$P = 2.74\ C_a + F_g \cdot C_g$$

where F_g varies with the A/G ratio and the total protein concentration. This equation has been tested on the colloid osmotic pressures of human and bovine plasma obtained in this Laboratory and the data of Weiss and Peters (human). It has been found to give satisfactory predictions (standard deviation = $\pm$2.9 mm. Hg).

Alloxan-induced diabetes in rats. E. THOROGOOD (introduced by E. B. Astwood). *Depts. of Pharmacology and Medicine, Harvard Medical School, Boston, Mass.* Observations on rats treated with alloxan monohydrate have confirmed recent reports that alloxan parenterally administered to various laboratory animals injures pancreatic insular tissue and induces symptoms of diabetes: hyperglycemia, glycosuria, polyuria, polydipsia, with or without ketonuria.

Of 10 rats receiving subcutaneously in divided dosage a daily total of 20 mgm. per hundred grams body weight of alloxan for one to four days, 3 developed glycosuria by the eighth day. Of these, a female bore a normal litter and is alive after 172 days, excreting approximately 4 grams of sugar daily; a male recovered within two months and reacted negatively to a series of stilbestrol injections. The third developed an infection and was discarded. Five of the group appeared unaffected; two died on the fourth day with findings indeterminate. Of 50 rats receiving one injection of 20 mg. per hundred grams, 30 died within a week, 10 were unaffected, and 10 developed a characteristic, prolonged, diabetic course terminating in dehydration, anuria and death. Of 6 rats receiving one-half this dose, 5 were unaffected. The sixth followed a cyclic course, excreting for the first two months a daily average of 6 grams of sugar, during the third month—0.8 gram, and at the start of the fourth—4 grams. Of 6 rats receiving daily 5 mg. per hundred grams, 4 exhibited glycosuria in four weeks.

Compounds of related chemical structure including uric acid, violuric acid, uramil, parabanic acid, benzalbarbituric acid, and 4-amino, 2-thiouracil failed to produce comparable effects.

Antithromboplastin (or anticephalin) activity of normal and hemophilic plasmas. LEANDRO M. TOCANTINS. *Division of Hematology, Dept. of Medicine, Jefferson Medical College, Philadelphia.* The clot delaying effect of incubation of plasma with homologous tissue extracts is only an underestimation of plasma antithromboplastin activity. Since it is the cephalin moiety of the thromboplastic lipoprotein that is vulnerable to the plasma antithromboplastin (Tocantins—Proc. Soc. Exp. Bio. and Med. **54:** 94, 1943), the response of a given plasma to a standard solution of human cephalin may serve as an indication of the antithromboplastin (or anticephalin) activity of that plasma, other factors being equal or under control.

Dilution of plasma (up to 20 per cent) reduces its anticephalin content and enhances the clot accelerating action of the cephalin, even though prothrombin is simultaneously reduced. Extreme dilution diminishes and eventually effaces the difference in behavior toward cephalin between normal and hemophilic plasmas. Certain standard solutions of cephalin must be diluted 40 to 60 times in order to produce on normal plasma the delayed clotting time observed on hemophilic plasma treated with the undiluted cephalin.

Anticephalin is removed from both plasmas by dialysis (1 part plasma vs. 50 parts H_2O, closed Visking 8/32 "Nojax" casings, 12 hours.), or contact for 3–4 hours (10 mgms. per cc. plasma) with infusorial earth, asbestos fibres, pumice stone or "filter cell."

Effect of epinephrine on the synthesis of acetylcholine. CLARA TORDA and HAROLD G. WOLFF. *New York Hospital and the Depts. of Medicine (Neurology) and Psychiatry, Cornell Univ. Medical College, New York, N. Y.* Stimulation of the sympathetic nervous system or administration of epinephrine is often followed by evidence of stimulation of the parasympathetic nervous system. Epinephrine inhibits choline esterase (Waelsch and Rackow, Science **96:** 386, 1942) producing an increased effectiveness of acetylcholine. In the following it was ascertained whether the presence of epinephrine modifies the synthesis of acetylcholine *in vitro*.

The synthesis of acetylcholine was studied following the method of Quastel, Tennenbaum and Wheatley (Biochem. J. **30:** 1668, 1937). Uniform samples of homogenized fresh frog brains were used as a source of the enzyme, while human serum or human spinal fluid and the frog brain itself supplied the substrate. The amount of free and total acetylcholine synthesized in the presence or absence of epinephrine was assayed biologically using the sensitized rectus abdominis muscle of frog.

Epinephrine in concentrations from 1.10^{-8} increased the synthesis of acetylcholine by 40 to 250 per cent above the control. This increase in synthesis is probably due to the property of epinephrine to form a reversible redox system.

Assuming that similar events may occur in the body, it is likely that the succession of manifestations of stimulation of the sympathetic nervous system by evidence of stimulation of the parasympathetic nervous system is due to both an increase in synthesis of acetylcholine, and an inhibition of choline esterase.

Effect of vitamine B_1 and related compounds on the striated muscle. CLARA TORDA and HAROLD G. WOLFF. *New York Hospital and the Depts. of Medicine (Neurology) and Psychiatry, Cornell Univ. Medical College, New York, N. Y.* Minz (Compt. rend. soc. biol. **127:** 1251, 1938) observed that cholinergic nerves liberate both thiamine chloride and acetylcholine when stimulated. From this observation v. Muralt (Naturvis. **27:** 265, 1939) postulated that vitamine B_1 may have some direct effect on the contraction of striated muscles following the stimulation of the motor nerves. Acetylcholine and thiamine chloride may have similar effects as both are quaternary ammonium compounds containing a free hydroxyl group. Furthermore vitamine B_1 is a competitive inhibitor of the choline esterase (Glick and Antropol, Proc. Soc. Exper. Biol. and Med. **42:** 396, 1939). The purpose of the following investigation was to ascertain whether vitamine B_1 and related compounds have a direct effect on one of the effector cells, the striated muscle of frog, and whether they modify the contraction induced by chemical agents such as acetylcholine and potassium.

Thiamine chloride, thiamine pyrophosphate, and acetylthiamine do not induce a contraction of the muscle in concentrations lower than 5.10^{-3}M in a period of 3 minutes. Low concentrations do not increase the effect of acetylcholine in inducing muscle contraction; higher concentrations may depress the effect of acetylcholine, suggesting that the thiamine compounds interfere with the action of acetylcholine.

The thiamine compounds in concentrations from 1.10^{-7} to 5.10^{-3}M increase the effect of potassium in inducing muscle contraction. This effect is probably due to the action of thiamine compounds on the metabolism of muscle.

The above observations may throw some light on the mechanism of action of vitamine B_1 in regulating the contraction of muscle.

Effects of referred somatic pain on structures in the reference zone. JANET TRAVELL, CHARLES BERRY and NOLTON BIGELOW (introduced by McKeen Cattell). *Depts. of Pharmacology and Anatomy, Cornell Univ. Medical College, New York, N. Y.* Skeletal muscles may exhibit "trigger points" or tender areas, pressure on which induces referred pain.

Lewis and Kellgren showed that referred somatic pain following injection of hypertonic saline produces tonic contraction of muscles in the reference zone. We have demonstrated that this phenomenon applies to referred pain induced by pressure on spontaneous "trigger points." In these experiments action potentials, recorded by the cathod ray oscillograph from electrodes inserted into a muscle (deltoid) in the reference zone, always appeared in association with a pain over the front of the shoulder induced by pressure on an irritable infraspinatus muscle, although the subject was able to relax completely as shown by absence of action potentials from other muscles in the arm (biceps and triceps) not in the reference zone.

The amplitude of pulsation of the temporal arteries was measured by means of a tambour in five subjects with "trigger points" in the neck muscles which gave pain referred to the forehead or to the temple. Pressure pain was associated with vasoconstriction of the temporal artery on the side to which it was referred, and release of pressure with immediate disappearance of pain and a transient vasodilatation. The temporal artery on the side opposite from the referred pain was similarly constricted, but there was no subsequent vasodilatation. Pain in the arm produced by ischemia, needling or pressure on a "trigger point" likewise produced vasoconstriction but negligible or no vasodilatation of the temporal artery.

Thus, referred muscle pain induced by pressure produces specific localized responses involving not only skeletal muscle but also arteries in the reference zone.

The effect of chromatolysis on oxygen consumption in the spinal cord of the guinea pig. ROBERT S. TURNER and MARGARET L. TURNER (introduced by V. E. Hall). *Dept. of Anatomy and Dept. of Physiology, Stanford Univ., Calif.* Using manometric methods, determinations were made of the oxygen consumption of segments L5 to S3 of the spinal cords of various groups of guinea pigs, as follows: 1, a normal control group; 2, a group in which bilateral chromatolysis of anterior motor horn cells had been induced by section of both sciatic nerves fifteen days previously; 3, a group in which the number of anterior motor horn cells had been depleted by bilateral section of the sciatic nerves three months previously; 4, a group in which unilateral chromatolysis had been induced by section fifteen days previously of the sciatic nerve of only one side; 5, a group in which the oxygen consumption was measured on the first, second, third, etc., day following bilateral section of the sciatic nerves. The group with bilateral chromatolysis showed a depression of oxygen consumption to a level significantly below the normal. Similarly, the group in which both sciatic nerves had been sectioned three months previously showed a depression of the same order of magnitude. In the group in which unilateral chromatolysis had been induced the oxygen consumption of both the chromatolysed halves and the unoperated halves of segments L5 to S3 fell within the range of values exhibited by the bilaterally chromatolysed group; comparison of the operated with the unoperated halves revealed a difference in oxygen consumption which was not statistically signifi-

cant. Twenty-four hours after bilateral section of the sciatic nerves the oxygen consumption of segments L5 to S3 fell within the normal range, at forty-eight hours it approached and at seventy-two hours it reached the depressed range seen in the group with bilateral chromatolysis. From these data it would appear that neither the number of chromatolyzed anterior motor horn cells of segments L5 to S3 as previously determined by Turner (J. Comp. Neurol. **79**: 73, 1943) nor the consequent decrease in actual number of these cells can adequately account for the lowered oxygen consumption observed fifteen days and ninety days, respectively, after section of the sciatic nerves.

The effect of anemic anoxia on peristalsis of the small and large intestine of the dog. EDWARD J. VAN LIERE, DAVID W. NORTHUP and J. CLIFFORD STICKNEY (by invitation). *Dept. of Physiology, School of Medicine, West Virginia Univ., Morgantown.* The colon of lightly barbitalized dogs was exposed by a midline incision, and the movements of the longitudinal muscles recorded. After a normal tracing had been obtained, the animals were subjected to successive hemorrhages as follows: 1.5, 0.7, 0.8 and 0.5 per cent of their body weight. Some animals withstood even greater hemorrhages. An interval was allowed between each bleeding, and most of the experiments were conducted over a period of about 4 hours.

In the majority of the animals the contractions of the muscles were affected, as evidenced by diminution in the height and frequency of contraction, after the animals had lost an amount of blood equivalent to about 2.2 per cent of their body weight. Severe hemorrhage practically abolished the contractions, although an occasional animal appeared to be highly resistant.

The effect of hemorrhage (20 per cent of the calculated blood volume) on the motility of the small intestine was studied on dogs. The experiments were rigidly controlled. A powdered charcoal-acacia mixture was given by stomach tube, and 30 minutes later the animal was sacrificed. In 8 control animals 54 per cent of the gut was traversed, and in 9 hemorrhaged animals 73 per cent. This suggests that the motility of the small intestine was increased following hemorrhage, but the figures were not statistically significant. Further work is in progress on this problem.

Kidney size in relation to hypertensive effect in experimental renal hypertension. G. E. WAKERLIN, W. G. Moss (by invitation) and M. L. GOLDBERG (by invitation). *Dept. of Physiology, Univ. of Illinois College of Medicine.* Despite good experimental evidence that renal blood flow may be normal in experimental renal hypertension following constriction of the renal arteries (Corcoran, A. C. and I. H. Page. Am. J. Physiol. **135**: 361, 1942), some clinicians treat selected hypertensive patients with one atrophic kidney by unilater nephrectomy on the false assumption that ren ischemia is basically involved in the mechanis of experimental renal hypertension.

We have studied the size of the kidney in rel tion to its hypertensive effect in six dogs wi moderate levels of hypertension following bilater renal artery constriction four to twelve mont previously. External palpation under anesthes or inspection at laparotomy showed one kidney be normal or near normal in size and the oth approximately two-thirds normal size. Removal the normal sized kidney from three of the do resulted in a prompt significant decrease in blo pressure in each case. Removal of the smaller ki ney from the other three dogs caused no significa change in their pressure levels. Both groups dogs were followed for four months subsequent nephrectomy.

The results of this preliminary study sugge that in experimental renal (Goldblatt) hyperte sion, a normal or near normal sized kidney more effective hypertensively than a moderatel atrophic kidney. [*Aided by a grant from the Joh and Mary R. Markle Foundation.*]

Treatment of spontaneous hypertension in the do with renal extracts. G. E. WAKERLIN, M. L. GOL BERG (by invitation) and W. G. Moss (by invita tion). *Dept. of Physiology, Univ. of Illinois Colle of Medicine.* One of us and others (Fed. Proc., 2 52, 1943) previously reported that the blood pres sures of two dogs with spontaneous hypertensio were significantly decreased by a four month course of partially purified hog renal extract co taining renin given daily and intramuscularly i a dose of 1 and 2 grams of fresh renal cortex equiva lent respectively per kgm. of body weight.

We have since treated one of these two hyperte sive dogs with a course of more highly purified ho renal extract containing renin in a 3 gram dose an later with hog liver extract prepared after th manner of partially purified hog renal extract in 3 gram dose. The second hypertensive dog ha since received a course of partially purified do renal extract containing renin in a 3 gram dose. third spontaneously hypertensive dog was given course of heat-inactivated partially purified ho renin in a 3 gram dose. With each course of treat ment there appeared to be a significant decrease i blood pressure with a gradual return to the pre treatment hypertensive levels during the three t five months following treatment. No toxic effect were observed.

The results suggest that spontaneous hyperten sion in the dog resembles experimental rena hypertension in the same species not only in it response to partially purified hog renal extrac containing renin but also in its response to mor highly purified hog renal extract containing reni

nd heat-inactivated partially purified hog renin oth of which are antihypertensive in experimental renal hypertension (Fed. Proc. 2: 51, 1943). The results also suggest that spontaneous hypertension in the dog is more responsive to tissue extracts than experimental renal hypertension since, contrary to the former, the latter hypertension showed no therapeutic response to the partially purified dog renal extract or to the hog liver extract (Fed. Proc. 2: 51, 1943). [*Aided by grants from the John and Mary R. Markle Foundation and Parke, Davis and Company.*]

Proximo-distal fluid convection in nerves, demonstrated by radioactive tracer substances. PAUL WEISS, HSI WANG (by invitation), A. CECIL TAYLOR (by invitation) and MAC V. EDDS, JR. (by invitation). *Dept. of Zoology, The Univ. of Chicago.* Color indicators injected into rat nerves demonstrate a proximo-distal shift of the endoneurial diffusion field (see preceding note). Corroborative evidence was obtained in rat and guinea pig nerves with the use of radioactive sodium chloride and cupric chloride. A minute pellet of these substances was deposited by means of a micropipette inside the nerve in situ. After 3 to 48 hours, the nerves were excised, dried and cut into pieces of equal length (mostly 5 mm.). The concentration of radioactive contents at various distances from the injection site was determined by exposing these fragments successively to a Geiger counter. Usually fragments from identical levels of several nerves were lumped. Corrections were made for background radiation. Radiation intensities were then compared between proximal and distal samples equidistant from the injection point. In 33 out of 34 such pairs from 29 different nerves injected with cupric chloride, the distal samples contained significantly greater amounts of the substance than corresponding proximal samples. In 43 nerves injected with sodium chloride, the differential was in favor of the distal samples in 20 out of 21 pairs.

The results prove a gradual distad shift of the diffusion field in rat and guinea pig nerves. This shift occurs even in the absence of blood circulation, but not after cutting or excising the nerves. A rabbit nerve gave inconclusive results. [*Work done under contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Chicago; also aided by the Dr. Wallace C. and Clara A. Abbott Memorial Fund of the University of Chicago.*]

Proximo-distal fluid convection in nerves, demonstrated by color indicators. PAUL WEISS and HSI WANG (by invitation). *Dept. of Zoology, The Univ. of Chicago.* The proximo-distal seepage of endoneurial fluid, originally assumed from observations on edema in constricted nerve (Weiss 1943), has been more directly demonstrated by the following experiments on rat nerves.

Particles of Chinese ink, injected into intact nerves in the living animal, move farther distad than proximad (46 cases). More conspicuous differences were obtained with the Prussian Blue reaction. After receiving a localized injection of a minute amount of potassium ferrocyanide, the nerve was left in situ for several hours, then excised and transferred to ferric chloride for Prussian Blue assay of the spread of the injected substance. Of 31 nerves examined between ½ and 3½ hours, 11 showed symmetrical diffusion, 2 a slight proximal excess, and 18 a markedly greater spread distad than proximad (averaging 7.1 and 3.8 mm., respectively). Nerves transected, ligated or excised at the time of injection developed no such differential.

In further experiments, a solid crystal of potassium ferrocyanide (cca. 0.1 mg.) was embedded in the nerve; otherwise same treatment as before. Of 51 treated nerves, 4 showed a slight proximal surplus. The remaining 47 gave the results listed below. The table also lists 28 control experiments with nerves cut at the time of injection.

	Hours after injection	No. of cases	Average diffusion		
			Proximal (P) (mm.)	Distal (D) (mm.)	Difference (D − P) (mm.)
Nerve intact (exper.)	0-3	27	3.8	6.7	*2.9*
	3-9	20	3.2	10.8	*7.6*
Nerve cut (control)	0-3	15	5.7	5.5	−0.2
	3-6	13	7.7	7.8	0.1

The figures demonstrate the gradual distad shift of the whole diffusion field in the intact nerve at a rate of cca. 1 mm. per hour. [*Work done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Chicago; also aided by the Dr. Wallace C. and Clara A. Abbott Memorial Fund of the Univ. of Chicago.*]

Urinary and salivary flows under desert conditions. J. H. WILLS and J. J. KELLY (by invitation). *Depts. of Physiology and of Biochemistry and Pharmacology, School of Medicine and Dentistry, The Univ. of Rochester, Rochester, N. Y.* Men drinking tap water *ad libitum* during laboratory exposures to high temperature (112° to 125°F.) and low relative humidity (6 to 20 per cent) lost an average of 1.5 per cent of their initial body weights, and produced daily an average of 709 mls. of urine; men deprived of water during the same exposure, and accordingly losing up to 11 per cent

of their body weights, had an average daily urinary volume of 714 mls. Urine flow decreased and urine specific gravity increased with exposure to heat. Dehydrations ranging from two to eleven per cent of body weight had no progressive effects on urine flow and specific gravity.

Men living under conditions of high temperature and low relative humidity either in the desert or in the laboratory had 24-hour urines of low volume (av. 907 mls.) and high specific gravity (av. 1.028). This may indicate that such an environment results in an unrecognized deficit of body water, so that men living in the desert are always slightly dehydrated.

Stimulated salivary rate (paraffin chewing) varied inversely with deficit of body weight (correlation coefficient of 0.74), and seemed to approach zero at a dehydration of about 8 per cent. The secretion of saliva by dehydrated men could be increased markedly by oral administration of pilocarpine but without significant alleviation of thirst, indicating that this sensation is not caused by pharyngeal dryness alone.

Salivary flow is believed to be a useful index of loss of weight by the body during dehydration, whereas urine flow and specific gravity are thought to have little value as indices of deficit of body water. [*Work done under contract, sponsored by CMR, between OSRD and The Univ. of Rochester. Field studies were made possible by various units of the U. S. Army.*]

Effects of "nitrite" vasodilators on blood pressure. J. H. WILLS, J. C. WEAVER (by invitation) and H. C. HODGE. *Dept. of Biochemistry and Pharmacology, School of Medicine and Dentistry, The Univ. of Rochester, Rochester, N. Y.* Sodium nitrite, nitroglycerine, erythrol tetranitrate, mannitol hexanitrate and a placebo were each given orally in usual clinical doses to patients with normal and elevated blood pressures. Blood pressure determinations were made at brief intervals until the effect of the drug was over. Fifty-one per cent of the patients given drugs had a fall of systolic pressure, while only 23 per cent showed a lowering of diastolic. The systolic fall was usually greater than the diastolic. None of the subjects had any significant change after the placebo.

The table summarizes the effects of the four drugs on the systolic pressure of hypertensive patients. The average fall in the blood pressure of normal patients after a drug was up to 10 mm. less than the corresponding figure for hypertensive ones.

Drug	Dose (gm.)	Fall (mm.)	Latency (mins.)	Duration (mins.)
Sodium nitrite	0.13	21	7	62
Nitroglycerine	0.006	16	2	20
Erythrol tetranitrate	0.016	14	35	256
Mannitol hexanitrate	0.032	12	55	252

In contradistinction to this wide variation of effect on oral administration, intravenous injection of 1 mg/kg of the same four drugs into cats produced falls in blood pressure of approximately the same latency, intensity and duration. Therefore, these four drugs are equally active once they are in the blood stream, and the differences on oral administration probably result from differences in absorbability from the intestine.

Brain changes after asphyxiation at birth. W. F. WINDLE, R. F. BECKER and ARTHUR WEIL (by invitation). *Inst. of Neurology and Dept. of Anatomy, Northwestern Univ. Medical School, Chicago.* Seventy guinea pigs were asphyxiated and resuscitated at birth. The brains of these and 5 normal littermate controls were sectioned serially and stained by a method permitting accurate histologic comparison.

Hemorrhages occurred in brains of all, 3 hours to 5 days after resuscitation, but in none killed by asphyxia. Edema appeared to be present between 8 hours and 4 days after resuscitation. Hemorrhage and edema apparently were not primary causes of neuron damage. Nerve cell changes, including peripheral vacuolization and chromatolysis occurred in all specimens between 1½ hours and 2 days. Marked cytopathology was often circumscribed. Cerebellum and corpus striatum were not severely affected, but thalamus, cerebral cortex, tegmentum and spinal cord were often badly damaged. A transient microglia proliferation took place at 2 to 21 days. Generalized or regional atrophy followed neuron destruction in two-thirds of severely asphyxiated, and half the mildly asphyxiated animals.

It was concluded that experimental asphyxiation followed by successful resuscitation of guinea pigs at birth produced neuropathologic changes of variable degrees of severity in all specimens studied 1½ hours to 3 weeks after birth, and produced detectable permanent structural changes in more than half of those allowed to live for more than 3 weeks. [*Aided by grants from The Women's Faculty Club and Medical Abbott Fund of Northwestern Univ. Medical School.*]

Thalamic damage after asphyxiation at birth. W. F. WINDLE, R. F. BECKER and ELSIE F. HUNTER (by invitation). *Inst. of Neurology and Dept. of Anatomy, Northwestern Univ. Medical School, Chicago.* Brains of 60 guinea pigs, asphyxiated and resuscitated at birth and killed 2 hours to 3 months later, showed pathologic changes in various regions. The thalamus and geniculate bodies were damaged more consistantly than any other parts. In 17 animals, marked changes were encountered there without apparent damage in corpus striatum or cortex. In 5 of these, unilateral

or bilateral hemorrhages were found about the anterior thalamic vessels. These brains and those without hemorrhages showed large areas of nerve-cell degeneration beginning in the anterior region, extending into the posterior and ventral, encroaching upon or involving most of the geniculate bodies, but sparing the medial parts of the thalamus and most of the hypothalamus. All of the cytopathologic changes were bilateral.

Correlated with structural defects certain motor and sensory symptoms appeared consistently. During the acute period these animals showed tremor, ataxia, incoördination, chorioathetosis, hyperesthesia and were extremely irritable. They lacked startle and nuzzle reflexes, the latter essential for nursing. Before they could right they lay upon their sides with limbs on which they lay extended and opposite limbs flexed. Recovery from motor symptoms was gradual. Hyperirritability soon subsided and hypoesthesia appeared as a permanent condition. Somnolence was usually observed and was often marked. Correlated with geniculate damage were defects in hearing and vision. [*Aided by grants from The Women's Faculty Club and Medical Abbott Fund of Northwestern Univ. Medical School.*]

Structural alterations in the brain in and after experimental concussion. W. F. WINDLE, R. A. GROAT (by invitation) and C. A. FOX (by invitation). *Inst. of Neurology, Northwestern Univ. Medical School, Chicago.* Concussions, without fracture and usually without hemorrhage, were produced in guinea pigs by striking the movable head. Controlled histopathologic studies were made at intervals up to 32 days thereafter. Immediate anatomical changes were demonstrated by perfusing with formalin a few seconds after striking a concussive blow. Nissl bodies of certain neurons became disorganized, some fragmented and others agglutinated, and the normal pattern or arrangement was significantly altered.

Chromatolysis began to appear 24 hours after concussion, became very marked by 6 days. It differed from that seen in ischemia or after axon section. No pathologic changes were observed in nerve roots or tracts after concussion. Cells of cerebrum, basal ganglia, thalamus, cerebellar cortex and sensory ganglia appeared to be unaffected. Only in one instance did an occasional primary motor neuron of cranial nerve nuclei show change. However, a few cervical anterior horn cells were chromatolyzed after very strong simple concussions. Marked degeneration took place in scattered large interneurons of the tegmentum of midbrain, pons and medulla oblongata, of Deiter's red and spinal trigeminal nuclei. Other vestibular, cochlear and central cerebellar nuclei were affected after very strong blows. Extent and amount of damage varied with severity of concussion. Several less severe blows caused as much change as a single strong blow. [*The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Northwestern Univ.*]

Additional observations on a "second" somatic receiving area in the cerebral cortex of the monkey. CLINTON N. WOOLSEY, *Dept. of Physiology, School of Medicine, Johns Hopkins Univ., Baltimore, Md.* In a previous note (Fed. Proc., 1943) we reported that a "second" somatic receiving area, homologous to Adrian's "second" somatic receiving area in the anterior ectosylvian gyrus of the cat, had been found in the monkey on the superior bank of the Sylvian fissure posterior to the insula in close relationship to the auditory area. The area is contiguous to area 7 of the posterior parietal gyrus. It was reported that in cat and dog the area received impulses from both sides of the body, chiefly from the apices but also from proximal parts of the limbs in response to movement of hairs or, under deeper anesthesia, to pressure. In monkey contralateral responses only were found and only in response to pressure applied to digits or to skin overlying muscles activating them.

In additional experiments on the monkey we have found that hair movement alone is sufficient to evoke responses in the "second" area provided the animal is under rather light anesthesia. Under this condition responses are produced both by contralateral and by ipsilateral stimulation. In the monkey responses can be evoked in areas *3*, *1* and *2* of Brodmann under anesthesia too deep for production of responses in the "second" somatic area. In the cat the opposite obtains and "second" area responses can be evoked in animals too deeply anesthetized for elicitation of responses in the primary area. In the cat latency is shorter for the "second" area response; in the monkey latency is shorter for the primary area response.

Compensatory renal hypertrophy after unilateral nephrectomy in thyroidectomized rats, considered in relation to histological changes in the pituitary. ISOLDE T. ZECKWER. *Dept. of Pathology, Univ. of Pennsylvania Medical School.* Evidence in the literature indicates that compensatory kidney growth after unilateral nephrectomy depends upon pituitary function. Thyroidectomy is known to reduce the number of acidophiles.

Twelve groups of rats were studied, each group consisting of 4 litter-mate males: 1, intact; 2, left nephrectomized; 3, thyroidectomized; 4, thyroidectomized with left nephrectomy. One adrenal and/or one testis was also removed to place extra burden of secretion on the pituitary. Compensatory hypertrophy was calculated as weight of right kidney of rat 2 over weight of right kidney of rat 1, and of 4 over 3, as factors of increase, for

which the mean values were 1.43 for rats with thyroids intact, and 1.41 for thyroidectomized rats. These are not significant differences. Therefore, although thyroidectomy reduced the weight of kidneys, when body kidneys were present, it did not alter significantly the compensatory hypertrophy. This supports the results of McQueen-Williams and Thompson who determined compensatory hypertrophy by a different method.

The hypothesis previously suggested by the author that stunting of visceral growth in thyroidectomized rats may be ascribed to acidophile loss must be modified now in view of this evidence that compensatory kidney growth can occur with reduced acidophiles, and in view of evidence that growth hormone administration does not benefit the hypothyroid individual, whereas administration of thyroid extract restores structure and function of the pituitary in the thyroidectomized animal.

The reactions of growing chicks to diets varying in salt content. R. P. Zimmer, J. S. Barlow and S. J. Slinger (introduced by J. F. Manery). *Depts. of Poultry Husbandry and Animal Nutrition, Ontario Agricultural College, Guelph, Canada.* For these experiments newly hatched Barred Plymouth Rock chicks were reared to 9 weeks of age on diets to which salt had been added in amounts varying from 0 to 10%. Twelve groups of birds were used, each group consisting of 16 males and 16 females. Records were kept of their weights and their consumption of food, water, oyster shell, bone meal and grit, all of which were supplied ad libitum. The death rate was noted and at 9 weeks 10 birds were sacrificed and their tissues analyzed.

The number of survivals was least in the group receiving the 8% salt diet undoubtedly due to the fact that their total intake was appreciably higher than in any other group. The consumption of oyster shell, bone meal and grit, which are largely calcium and magnesium carbonate and phosphate, and also the water intake increased almost linearly as the salt content rose, until about 6% at which time a "breaking point" was observed in this type of compensation.

The concentration of chloride in skin, tendon and kidney almost doubled. There was also some increase in chloride in the lung and the liver, a slight change in skeletal muscle but an actual fall in heart muscle chloride.

THE AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS

Abstracts of papers received from the Secretary of the Society. Since there will be no meeting in 1944 these papers are to be regarded as "read by title". For possible corrections in any of these abstracts see the next issue.

Absorption of quinine from isolated intestinal loops. James C. Andrews and W. E. Cornatzer (by invitation). *Dept. of Biological Chemistry and Nutrition, School of Medicine, Univ. of North Carolina, Chapel Hill.* Comparisons of the rate of absorption of quinine in the forms of the free base, the hydrochloride and the sulfate under various conditions from isolated intestinal loops of dogs have led to the following conclusions:

Within short periods (up to 30 minutes) the dihydrochloride is absorbed two to three times as rapidly as the sulfate. In experiments of sixty and ninety minutes the difference between the two salts is much smaller. That this difference is not a simple result of water solubility is indicated by two findings. Administration of the quinine sulfate in solution in physiological saline, in which it is much more soluble than in water, has no effect on its speed of absorption. Higher concentrations of sodium chloride, although they increase the solubility of the quinine sulfate up to a maximum at about 4% NaCl, decrease the rate of absorption. Furthermore the free base, with its very low water solubility, is much more quickly absorbed than is the sulfate and, in fact, leaves the loop nearly as rapidly as does the dihydrochloride. The pH of the contents of the loop is not sufficiently low to convert any appreciable portion of the base into a salt and even the simultaneous addition of equivalent amounts of sodium sulfate with the free base does not decrease the rate of absorption. [*Supported by a grant from the Samuel S. Fels Fund.*]

Denaturation of the gonadotropins by urea. Fritz Bischoff. *Santa Barbara Cottage Hospital Inst., Santa Barbara, Calif.* The rate of inactivation of the physiologic activity of human chorionic, sheep pituitary, and mare serum hormones in 40 per cent urea concentration at 37.5°C. was studied. The inactivation of the chorionic gonadotropin proceeded rapidly and was independent of concentration of hormone, but the rate was such that a first order reaction could only be

assumed on the basis that the reaction product was a stable substance of lesser biologic activity. Chorionic gonadotropin partially inactivated by standing in aqueous solution at room temperature was more rapidly inactivated by urea than the original hormone. The mare serum hormone manifested a remarkable degree of stability. The inactivation of the sheep pituitary gonadotropin proceeded less rapidly than that of the chorionic gonadotropin and was somewhat dependent upon concentration.

Relationship between protein intake and pyridoxine deficiency in the rat. The rôle of tryptophane and cystine. LEOPOLD R. CERECEDO and JOHN R. FOY (by invitation). *Dept. of Chemistry, Fordham Univ., New York City.* In a previous communication (Proc. Div. Biol. Chem., Amer. Chem. Soc., Atlantic City, 1941), it was shown that the level of protein in the diet has a pronounced effect on the severity of symptoms of pyridoxine deficiency in the rat. The dermatitis that developed on a low protein diet was a mild form in most cases, whereas in the animals receiving the higher protein levels, severe symptoms developed.

A possible connection between tryptophane and the effects of a high protein intake was suggested by the experiments of Lepkovsky et al. (J. Biol. Chem. **149:** 195, 1943), who isolated xanthurenic acid from the urine of pyridoxine-deficient rats, and showed that it was derived from dietary tryptophane. These findings indicated a derangement of tryptophane metabolism.

With a view to ascertaining the rôle of tryptophane and cystine in the development of pyridoxine deficiency, the following experiments were carried out. One group of rats, which served as controls, received the low-protein (15 per cent) ration (diet A). A second group received diet A supplemented with tryptophane in an amount equivalent to that present in a diet containing 60 per cent of casein. In these animals, the symptoms appeared at a later period than in the controls. They also lived longer. A third group receiving diet A supplemented with cystine developed more severe symptoms than the controls. A fourth group were given diet A supplemented with tryptophane and cystine. In this case, the tryptophane had some protective action, but it was not sufficient to neutralize completely the effect of cystine. [*Aided by a grant from the Committee on Scientific Research of the American Medical Association*].

Vitamin E deficiency in the mouse. LEOPOLD R. CERECEDO and LEONARD J. VINSON (by invitation). *Dept. of Chemistry, Fordham Univ., New York City.* Symptoms such as muscular paralysis and incoordination of the forelegs and head, have been observed in rats on vitamin E deficient diets. Attempts to obtain similar manifestations in mice have hitherto failed. We have observed numerous cases of incoordination in young mice from females reared on a diet having the following percentage composition: Casein, 17; salts, 5; Crisco, 4; lard, 3; cod liver oil, 3; sucrose, 58; and brewers' yeast, 10. The dyndrome is characterized by a tilting of the head to one side, inability to run in a straight line, and a frequent tendency to move backwards. In some animals, muscular paralysis developed just before weaning. In several cases, these symptoms disappeared after weaning, but for the most part they remained throughout life. Administration of alpha-tocopherol, 20 mg. per kilo of diet, prevented almost entirely the development of symptoms. Increasing the protein of the diet to 25 per cent had a similar effect.

Of a total of 27 litters weaned on the basal diet, 15 contained young showing vitamin E deficiency, whereas of 17 litters weaned on the basal diet supplemented with vitamin E, only 2 exhibited the symptoms, and of 11 litters weaned on the 25 per cent casein diet, only 3 showed signs of vitamin E deficiency. The effect of the increased protein intake is interesting, since it indicates that previous failures to obtain symptoms in vitamin E-deficient mice may be related to the high protein level in the diets used. Our findings suggest a relationship between vitamin E and protein metabolism.

The influence of insulin and the ions of sodium and potassium on the consumption of oxygen by liver slices. RALPH C. CORLEY and DELBERT M. BERGENSTAL (by invitation). *Dept. of Chemistry, Purdue Univ., Lafayette, Indiana.* The increase in the consumption of oxygen in Warburg flasks, by liver slices of white rats (fed or fasted), in the presence of pyruvate (concentration of substrate routinely 0.01 M), and the further increase with the additional presence of zinc-free insulin, have been found to be markedly influenced by the ratio of sodium ion to potassium ion, in the isotonic phosphate buffer solution (pH = 7.3) in which each is suspended. In the practicable absence of either Na or K, insulin had little or no effect on the rate of absorption of oxygen in the presence of pyruvate. The maximum effect was observed when Na:K = circa 16:1, although with pyruvate alone, TQO_2 was highest with a lower ratio of Na:K.

Essentially similar conclusions appear warranted for the experiments with succinate and with citrate.

When the ratio of Na to K was 4 to 1, there was with added insulin a further increase in the consumption of oxygen with hexosemonophosphate, hexosediphosphate, α-ketoglutarate, and oxaloacetate respectively, a slight (perhaps significant) increase with malate, but none with fumarate, butyrate, cis-aconitate, glycogen or glucose. In experiments similar except for the practicable

absence of Na, slight (perhaps significant) increases in the consumption of oxygen were observed with hexosemonophosphate, hexosediphosphate and α-ketoglutarate respectively, but not with oxaloacetate, fumarate, malate or butyrate.

Zinc-insulin has not been found to increase the consumption of oxygen in the presence of pyruvate.

It is suggested that the current lack of agreement concerning the influence of insulin in slices and other preparations of tissues, is attributable in some measure to differences in the inorganic composition of the suspending fluids employed by the several investigators.

Intravenously administered crystalline amino acids in causation of vomiting in dogs. WARREN M. COX, JR. AND ARTHUR J. MUELLER (by invitation). *Mead Johnson Labs., Evansville, Ind.* Intravenous injections of 0.24 gm. nitrogen per kilo as essential amino acids, and Amigen (casein hydrolysate), were made in two dogs. An equivalent amount of glycine replaced any amino acid omitted from Mixture VII[b].

Injection time[a]

Amino acid omitted	Dog. 1, 25 kg.			Dog 2, 20 kg.		
	2 hrs.	1 hr.	30 min.	2 hrs.	1 hr.	30 min.
Mixture VII[b]	V			V		
Amigen	=	=	V[c]	=	=	—[c]
dl-Threonine	—		—			
dl-Valine				V		
dl-Leucine	V		—[d]	⟷	V	
dl-Isoleucine	V				V	
dl-Lysine				V		
dl-Tryptophane	—	—	—	—	V	V
dl-Phenylalanine			—	V		
dl-Methionine			—	—	=	V
dl-Methionine & glycine					⟷	
l-Histidine HCl	⟷	⟷	—	V		
l-Arginine HCl				—	V	
Mixture VII[e]	⟷	V			V	
Amigen[e]		—	V		—	V

[a] Symbols: V = vomiting; ↔ = nausea; — = no effect.
[b] Madden, et al., J. Exper. Med., 77, 277 (1943)
[c] 45 min. injection.
[d] Dog apparently learned to tolerate injections.
[e] Injected at end of series for comparison.

As the study progressed, Dog 1 did not vomit on previously unsatisfactory mixtures (e.g., leucine-free). Dog 2 vomited with all mixtures except that the methionine-free one was tolerated best. Casein hydrolysate caused less vomiting than the mixed ten crystalline acids. Since no one amino acid was found causative of vomiting, it is believed that the unnatural isomeric forms are responsible.

Amino acids in the potato (Solanum tuberosum). FRANK A. CSONKA and H. LICHTENSTEIN (by invitation). *Bureau of Human Nutrition and Home Economics, Agricultural Research Administration, U. S. Dept. of Agriculture, Washington.* In the determination of amino acids in the whole potato, we observed an exceptionally high content of tyrosine, which, if present entirely in the protein of the potato, would represent an unusually high percentage (7 to 10 per cent). It was found, however, that part of the tyrosine is present in free form in the press juice.

The whole potato was mashed under 2 N sulfuric acid; the acid extracts adjusted to 5 N were hydrolyzed and showed 62 mg. of tyrosine (Folin-Ciocalteu) per 100 gm. of potato. When the potato was pressed and the press cake extracted by water followed by salt solution (1 per cent) the tyrosine content was 42 mg. In the acid immersion method where tyrosinase activity was eliminated the tyrosine value is 50 per cent higher than that obtained in the press juices. The press juice contained 20 mg. of free tyrosine per 100 gm. of potato as determined in the filtrate remaining after coagulating the protein by heat. When the press juice was dialyzed, and the dialysate extracted by butyl alcohol (Dakin), tyrosine crystals were easily distinguishable under the microscope. The difference between the values for tyrosine obtained on one aliquot of juice heated immediately after pressing and another aerated without inactivation agreed with that for free tyrosine. Tyrosinase affects only free and not the peptide-bound tyrosine.

Colorimetric determinations also indicated that out of 28 mg. of tryptophane found in 100 gm. of potato 15 mg. are present in free form, assuming that none of the color was due to an indole product resulting from tyrosinase activity.

The content of water, chloride, total nitrogen and collagen nitrogen in tendons of the dog. LILLIAN EICHELBERGER and JEAN D. BROWN (by invitation) *Dept. of Medicine, Univ. of Chicago.* The right and left Achilles tendons and the tendons of the flexor and extensor muscles of the front legs were removed from eight dogs for analyses of total fat, total water, chloride, total nitrogen and collagen nitrogen. Wide deviations in the concentrations of these constituents were found in different sections of the individual tendons. Nevertheless the average of all of the analytical values for each constituent of the tendon was practically the same for every animal. It appears probable therefore that at different levels of the tendon there are present different sense organs, blood vessels, fascia, etc. which would account for the variations in the content of fat, water and nitrogen in the different sections of each individual tendon.

For the Achilles tendons the means were found to be as follows: total water, 610.7 ± 1.04 g.; chloride, 77.2 ± 3.2 mM; total nitrogen, 67.8 ± 3.3 g.; collagen nitrogen, 61.0 ± 3.2 g. per kilo of fat-free tendon. For the frontal tendons the means

were: total water, 602.8 ± 1.41 g.; chloride, 79.1 ± 3.2 mM; total nitrogen 67.1 ± 3.2 g., and collagen nitrogen 63.1 ± 2.2 g. per kilo of fat-free tendon.

Response of the gastrointestinal tract to ingested glucose. PAUL F. FENTON (by invitation) and HAROLD B. PIERCE. *Dept. of Physiological Chemistry, College of Medicine, Univ. of Vermont, Burlington.* The methods used in these studies on rats have been reported previously (J. Biol. Chem. **133:** xxxi, 1940). Numerous additional experiments have since confirmed our findings that the emptying rate of the stomach decreased progressively as greater concentrations of glucose were fed, that the rate of absorption increased significantly with the concentration fed, that the volume of acid gastric secretion decreased with increasing concentration but that very high concentrations elicited a copious secretion of slightly alkaline fluid.

It was found that gastric secretion, gastric emptying and intestinal absorption were most rapid during the quarter hour following administration of the glucose solutions ranging from 5.5 to 65 per cent in concentration. When concentrated glucose solutions were fed, an inhibition of gastric emptying began shortly after glucose injection. Although emptying was gradually resumed, it remained slow during the remainder of the first hour. Rats weighing between 145 and 283 grams absorbed 50 per cent glucose at the same rate, while younger and lighter animals absorbed glucose more slowly. The decrease was by no means proportional to the body weight. A group of rats averaging 246 grams in weight absorbed 261 milligrams of glucose while another group weighing 129 grams absorbed 224 milligrams in one hour. It was found, in agreement with others, that glucose absorption was slower after a 48 hour fast than after a 24 hour fast. The depression due to fasting was more pronounced in the male than in the female.

Studies on anesthetized rats whose stomachs were ligated at the cardia and pylorus showed little or no gastric glucose absorption.

Molecular length of fibrinogen and zein as deduced from double refraction of flow. JOSEPH F. FOSTER (by invitation), HERBERT SCHEINBERG (by invitation) and JOHN T. EDSALL. *Dept. of Physical Chemistry, Harvard Medical School, Boston.* The orientation of elongated molecules, when subjected to a velocity gradient, can be deduced from the double refraction produced in the flowing solution. The velocity gradient required to produce a given degree of orientation, however, varies almost as the reciprocal cube of the molecular length. To study relatively short molecules, a concentric cylinder apparatus has been constructed which permits the attainment of velocity gradients up to 30,000 cm^{-1}.

Human fibrinogen,[1] prepared in this laboratory, has been studied in aqueous salt solution and in glycerol-water-salt mixtures. Earlier studies by Boehm and Signer, and Wöhlisch, demonstrated that fibrinogen shows flow birefringence, but did not permit calculation of molecular length. From our studies the length is deduced as 900 ± 200 Å. This estimate is in harmony with data on the viscosity increment of fibrinogen in solution, which is higher than that of any other blood protein, and with preliminary estimation of molecular weight.

Zein is a much shorter molecule than fibrinogen and must be studied in solvents of high viscosity to achieve satisfactory orientation. Propylene glycol and propylene glycol-ethanol mixtures have been employed as solvents. In these solvents, zein shows well marked double refraction of flow. The molecular length, in one preparation which has been intensively studied, is deduced as approximately 340 Å. This tentative estimate is in good agreement with the value of 320 Å, calculated by Neurath from sedimentation and diffusion. Another preparation made by a different method showed a somewhat greater molecular length.

Pituitary control of blood insulin level. H. FRAENKEL-CONRAT and J. FRAENKEL-CONRAT (by invitation). (*Formerly*) *Inst. of Experimental Biology, Univ. of California, Berkeley.* It is well established that dietary factors which influence the rate of insulin secretion cause corresponding changes in the pancreatic insulin content. Yet, in the cases of two pituitary hormones, recently shown to control the rat's pancreatic insulin (Am. J. Physiol. **135:** 404, 1942), there were no indications of increased gland content being associated with increased secretion, and vice versa. Actually, the reverse relationship seemed probable for the growth hormone, which while decreasing pancreatic insulin is generally believed to favor increased insulin secretion.

To estimate the rate of insulin secretion, blood insulin determinations were performed, using Gellhorn's method (Endocrinology **29:** 137, 849, 1941). The action of growth and lactogenic hormones on the blood insulin of hypophysectomized and normal rats was studied. While the observed changes were consistent, a greater number of experiments would be needed for the demonstration of statistical lgnificance, owing to the variability of blood sugar levels. Since this study had to be abandoned, it is here reported as a suggestion rather than an established finding. The results indicated that the rat's blood insulin level was 1) raised after hypophysectomy, 2) raised rapidly (within one hour) by growth hormone,

[1] Prepared under contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and Harvard University.

and 3) lowered (more slowly) by lactogenic hormone administration.

These findings suggest that growth hormone decreases pancreatic insulin by releasing the latter hormone into the circulation, while lactogenic hormone increases the gland content by favoring insulin storage, rather than secretion. Such findings indicate the need for caution in interpreting the physiological significance of the hormonal content of endocrine glands.

Substances which decrease the solubility of albumin S in human cancer. MARTIN E. HANKE, HERBERT KAHN (by invitation) and ROSE FELSHER (by invitation). *Dept. of Biochemistry, Univ. of Chicago.* Albumin S is defined as that fraction of the serum protein which remains dissolved at 41.5 g. per cent $(NH_4)_2SO_4$ at pH 6.8 in 1 to 250 dilution of serum. It is the most soluble albumin of blood and constitutes about six per cent of the total albumin. In human cancer albumin S values are decreased to less than half (often to one-fifth of normal) even when the total albumin is normal or three-fourths of normal; this holds similarly in obstructive jaundice, and the last three months of pregnancy.

Studies on the effect of the addition of chemical substances to serum in vitro have shown that bile acids (glycocholic taurocholic, and glyco-desoxycholic) markedly decrease the albumin S without corresponding effect on the total albumin; 0.15 mg. per ml. is appreciable, while at 5 mg. per ml., where the effect is maximal, the albumin S is decreased to one-tenth of its normal value. Fractionation of lipoid extracts of normal and cancer urines have shown in cancer urine 40 to 100 mg. per day of a neutral, non-saponifiable, benzene soluble material which is equally potent as bile salt in lowering albumin S levels; while normal urine contains only 5 to 15 mg. of such material. It is believed that the presence of these substances in cancer sera determines the low albumin S values found in such sera. It is thought that these cancer substances may interfere with the nutritive and vehicular functions of albumins for normal tissues.

Diet and blood thioneine. ROMAN HARKAWAY (by invitation) and WILLIAM M. CAHILL. *Dept. of Physiological Chemistry, Wayne Univ. College of Medicine, Detroit.* In the rat, blood thioneine is exogenous and its level is influenced by diet according to Potter and Franke (J. Nutr. **9:** 1, 1935). We have made an initial study on the influence of diet on blood thioneine in man. Determinations were made on the blood of a number of individuals, each of whom had for several days been consuming a particular type of diet. Thioneine was separated from uric acid by treatment of the blood filtrates with silver nitrate and acid lithium chloride solutions (Benedict and Behre, J. Biol. Chem. **92:** 161 1932) and the thioneine was estimated in the precipitate by the method of Behre and Benedict (J. Biol. Chem. **82:** 11, 1929). Thioneine used in the standards was prepared from ergot.

The experimental results follow: high protein diet, 4 individuals, 1.9–5.9 (3.8 av.) mg. thioneine per 100 cc. blood; low protein, 5 individuals, 0.0–6.3 (4.9 av.) mg.; high purine, 5 individuals, 1.5–5.9 (3.7 av.) mg.; low purine, 5 individuals, 2.9–5.9 (4.3 av.) mg.; fasting, 5 individuals, 3.3–5.2 (3.8 av.) mg. It is evident that the blood thioneine levels were subject to marked variations which, under our experimental conditions, could not be correlated with the general type of diet.

The experimental subjects were students who, unsupervised, ate suggested diets primarily for another purpose—a study of the influence of diet on the composition of urine—in connection with a laboratory course. A further study of this problem under carefully controlled dietary conditions and, if possible, with an improved analytical method remains to be carried out.

X-ray diffraction of muscles II. G. C. HENNY (by invitation), E. W. ASHKENAZ[1] (by invitation) and M. SPIEGEL-ADOLF. *Depts. of Physics and Colloid Chemistry, Temple Medical School, Philadelphia.* Our former studies (Fed. Proc. **2**), using a similar material and apparatus, were extended in different directions. Statistical evaluations of the measurements on moist and dried muscle ascertain the identity of most corresponding spacings and give evidence of only a small amount of intramolecularly bound water along the longitudinal axis. Resoaking of dried muscle is conducive to a complete reversal of the change produced by drying for 24 hours at room temperature in a desiccator. The x-ray diffraction pattern of such a resoaked muscle is identical with the one given by a living moist muscle.

Effects of single shock electric stimulation, consisting in disappearance of orientation of the x-ray diffraction pattern, become manifest only in a muscle which shortens markedly. Such changes are agsent in muscles contracting either isotonically or isometrically.

Of the different agents known to produce rigor in muscles, (heat, chloroform, death) heat alone produces characteristic changes of the x-ray diffraction pattern. These changes consist in a sharpening of the outside ring and in the appearance of a new ring corresponding to a spacing of 22 Å.

KCl, when used in concentrations at which NaCl apparently does not affect the x-ray diffraction pattern of muscle, produces characteristic changes in the latter. The orientation disappears to a great extent and a number of salt rings appear which can be identified with the diffraction pat

[1] Kathryn McHale Fellow, AAUW.

ern of KCl. In conformity with other experiences these findings are explained by an increase of membrane permeability caused by the specific effects of potassium ions.

Adsorption of phosphates by bone, dentin and enamel after prolonged exposure to phosphate solutions as shown by the radioactive isotope. E. GUNNAR JOHANSSON (by invitation) and HAROLD CARPENTER HODGE. *Dept. of Biochemistry and Pharmacology, School of Medicine and Dentistry, Univ. of Rochester, Rochester, N. Y.* Previous studies of the adsorption of various substances using radioactive isotopes as tracers have shown that after short periods of exposure to solutions bone adsorbs more than dentin which in turn adsorbs more than enamel. This order has been found for phosphates at 200°C and at 40°C, for fluorides, sodium and strontium at 40°C. It is believed that this order reflects a variation in some fundamental property of the tissues and at first it was attributed to the reported variation in particle size. The particles of bone are calculated to be about 10^{-6}cm., those in enamel about 10^{-4}cm. and those in dentin intermediate in size. Different limitations of penetration by the respective densities could also account for the order found.

Using phosphate solutions containing radioactive phosphorus as a tracer, long exposures (up to 64 hours) of powdered bone, dentin and enamel produce marked increase in the total phosphate absorbed by each tissue and, by the 64th hour, a reversal in the order of the amounts adsorbed so that enamel > dentine > bone. If diffusion is the controlling property, such a reversal would not be predicted. Particle size appears to be ruled out as an explanation. The reason for the order of amounts adsorbed after prolonged exposure is unknown.

Amino acid metabolism in diabetes mellitus. ALFRED E. KOEHLER, ELSIE HILL (by invitation) and ELLEN BUTTENWIESER (by invitation). *Sansum Clinic and Santa Barbara Cottage Hospital, Santa Barbara, Calif.* Repetition of our studies of glycine and alanine metabolism in diabetes (Fed. Proc. 2: No. 1, 64, 1943) using casein hydrolysate plus 1 per cent tryptophane give similar results. Thirty g. of the amino acids were injected at constant rate intravenously for 2 hours in 10 normal subjects and in 8 with uncontrolled diabetes. The blood amino acid levels and extra urea as well as the urinary excretions were essentially the same in the 2 groups.

There was, however, a quicker and a greater increase in extra ketones in the blood and urine in the diabetic group.

The blood sugar rise and, in the case of the diabetic group, the extra urine sugar after amino acid injection was similar to that after the injection of 20 g. of glucose. This indicates that if the extra sugar comes from the injected acids, the conversion was so rapid that it did not alter the time relationships.

The blood sugar rise after the animo acid injections equalled in the normal group 52 per cent and in the diabetic group 86 per cent of the rise after 20 g. of glucose. On this basis the normal person converts 35 per cent and the diabetic subject 57 per cent of the injected amino acid to glucose. The latter figure is in close agreement with the usually accepted figures of 55 to 62 per cent conversion of protein.

It appears that in diabetes sugar and ketones are formed more readily from amino acids than in normal subjects.

Alcohol and acetic acid metabolism in diabetes mellitus. ALFRED E. KOEHLER, ELSIE HILL (by invitation) and ELLEN BUTTENWIESER (by invitation). *Sansum Clinic and Santa Barbara Cottage Hospital, Santa Barbara, Calif.* The injection of 30 g. of ethyl alcohol intravenously at constant rate for 2 hours in 7 diabetic subjects resulted in blood alcohol levels and urine excretion that differed little when this same group was completely controlled with insulin, nor were the values significantly different from a group of 4 normal subjects.

The blood and urine extra ketones during and after alcohol injections were not appreciably or consistently altered in the diabetic group.

Alcohol caused no increase in blood or urine sugar in either the diabetic or normal subjects.

Blood and urine acetic acid was but little elevated after alcohol injection even though the alcohol was rapidly utilized. This at first seemed to indicate that alcohol oxidation did not go through the acetic acid stage. However, the injection of 30 g. of acetic acid ¾ neutralized under the same conditions showed it to be oxidized with such great rapidity in both diabetic and normal subjects that no appreciable rise after alcohol could be expected.

Ketone formation from acetic acid in the normal subject was not appreciable. In the diabetic subject with mild ketosis, more ketones were formed, but even here the extra ketones accounted for less than 4 per cent of the acetic acid injected. The indications are that acetic acid can be oxidized without ketone formation but possibly also under certain metabolic conditions, as in diabetes, ketones can be formed. This suggests that ketosis may not only be the result of excessive fat breakdown but of abnormal fatty acid oxidation.

Studies of urinary calcium excretion I. In normal persons. ELIZABETH L. KNAPP (by invitation) and GENEVIEVE STEARNS. *Dept. of Pediatrics, State Univ. of Iowa, Iowa City.* 606 studies of urinary calcium excretion in healthy persons 1 to 80 years old have been analyzed statistically. The data

were obtained from this laboratory (370 studies) and from the literature. The data include only studies of normal persons whose diets were of customary mixed composition, and wherein milk was used as the chief source of calcium.

Calcium intake and weight of the person are important in determining the quantity of urinary calcium. The major factor is endogenous, probably due to endocrine balance which aids in determining the percentage of intake excreted in urine. The relationships of the various factors may be expressed as an exponential equation. Given the daily calcium intake, urinary calcium and the weight of the person, the formulas for normal maximum (M), mean ($\bar{y}$) and minimum (m) $\frac{\text{urine Ca}}{\text{Ca intake}}$ are as follows. I represents calcium intake per kilogram body weight.

$$M = 365\ I^{-.801}$$
$$\bar{y} = 158.9\ I^{-.802}$$
$$m = 34.1\ I^{-.835}$$

These formulas hold for all ages, 1 to 80 years. Each person tends to maintain his position relative to the mean at all levels of intake studied and over a period of at least several years. It is probable that the relative position is somewhat altered by puberty.

Examination of 880 studies of urinary calcium in infancy shows that urinary calcium excretion of infants follows the same laws. The values observed lie within the range normal for older subjects, but the mean value is somewhat lower in infancy.

Studies of urinary calcium excretion. II. In endocrine disturbances. ELIZABETH L. KNAPP (by invitation) and GENEVIEVE STEARNS. *Dept. of Pediatrics, State Univ. of Iowa, Iowa City.* The urinary calcium excretion (Ca_U) of persons with increased or decreased activity of certain endocrine glands has been compared with that of normal persons (Knapp, E, L., and Stearns, G., preceding abstract). The data analyzed were from this laboratory and the literature.

In hyperparathyroidism, Ca_U is above the normal maximum at all levels of intake. After removal of the tumor, the Ca_U decreases to values below the normal mean; some values reported are below the normal minimum.

In hypoparathyroidism, Ca_U is below the normal minimum and increases to within normal range with increase in serum calcium.

In hyperthyroidism, Ca_U is similar to that observed in hyperparathyroidism; the increase may be even more marked. With therapy, the values become normal, rarely as low as during recovery from hyperparathyroidism.

In myxedema, Ca_U lies within the normal range, though below the normal mean. With therap Ca_U is increased to above the normal maximu These findings differ from the customary concep

During pregnancy, Ca_U tends to increase to maximum which occurs after the 20th and usuall after the 30th week. Few values rise above th normal range, but the mean is higher than th normal mean. In early lactation, Ca_U is below th normal mean, but within the normal range.

A 2 year old girl with precocious puberty showe a Ca_U above the normal maximum and a high tit of estrogen in urine. After removal of one ovar urinary estrogen decreased and Ca_U becam normal.

Iodination of thyroglobulin under conditio compatible with life. J. F. MCCLENDON and W C. FOSTER (by invitation). *Hahnemann Medic College, Philadelphia.* Two and seven-tenths gra of human thyroglobulin from a goiter (containi 0.06 per cent of thyroxine-iodine and 0.18 per ce of total iodine) was dissolved in a physiologic salt solution of 10 g. of NaCl and 5 g. of NaHC in 2 liters of water. To this was added 0.27 g. iodine crystals and the suspension was stirred in thermostat at 38°C. for 20 hours. The thyroglo ulin was precipitated by heat, washed with wat and dried. It was found to contain 0.342 per ce of thyroxine-iodine and 3.56 per cent of tot iodine, increases of 570 per cent and 1975 per ce respectively. These are higher values than we ha ever found in natural thyroglobulin. The iodi was determined by the McClendon-Bratt method (J. Biol. Chem. **123:** 699, 1938) and th thyroxine precipitated by a modified Haringto Randall method (J. Biol. Chem. **110:** 680, 193 Since tadpoles metamorphose after having iodi crystals implanted in their bodies, we consid the conditions of iodination of the thyroglobul compatible with life.

Protein-bound iodine in the blood corpuscles a plasma. J. F. MCCLENDON and WM. C. FOSTER (b invitation). *Research Lab. of Physiology, Hah mann Medical College, Philadelphia.* All the iodi determinations were made by the method McClendon and Bratton (J. Biol. Chem., 12 699, 1938). Comparison was made of three metho of separating the proteins: 1, by dialysis, 2, b zinc hydroxide (Somogyi) and 3, by the methan acetone method of McClendon and Foster (Pr Soc. Exp. Biol. Med., **39:** 230, 1938). The results micrograms of iodine per 100 cc. were as follow Dog A, (dialysis) plasma 5.4, corpuscles 4. (Somogyi) plasma 5.4, corpuscles 5.6, (McClendo Foster) plasma 4.2, corpuscles 5.0. Since there w no essential difference in the results by the thr methods and this point was confirmed by ma determinations on whole blood, the remainder the partitions were made by the McClendo Foster method as follows: Dog B, plasma 4.

rpuscles 5.5; cat serum 7.6, corpuscles 7.2; cow asma 6.8, corpuscles 6.4; man A, plasma 4.2, rpuscles 5.2; man B, plasma 5.0, corpuscles 4.9. he average value of protein-bound iodine for asma is 5.4 and for corpuscles is 5.5.

Conclusions: There is no great difference beeen the protein-bound iodine content of the rpuscles and plasma (or serum). Whether dinated protein exists inside the corpuscle or is erely attached to the outside is unknown. The ethanol-acetone method of McClendon and oster for precipitating the protein does not reove the iodine from the protein.

Quinine and vitamin B-complex deficiency. ILDRED MCEWEN and GRANVIL C. KYKER (inoduced by James C. Andrews). *Dept. of Biologil Chemistry and Nutrition, School of Medicine, niv. of North Carolina, Chapel Hill.* The inestigation reported herein under similar title st year was continued by a different procedure. he rat remained the experimental animal. The ose was increased from twenty to eighty millirams of quinine per kilogram body weight and as administered subcutaneously rather than ally. Doses were weekly rather than daily and ch was followed by twenty-four hour urine colction and determination of quinine. Quinine ctate instead of the hydrochloride was used to ovide less tendency for ulceration subsequent to d at the site of injection. Some animals became cerated with the lactate. Repeated comparisons rified the advantages of an improvised metabism cage with glass funnel over the standard etal cage.

Rats, thirty-five days of age, gave an increased xcretion of the dose as the animals progressed om a normal state to a severe B-complex itaminosis, the last excretion being approxiately fifty per cent greater than the first. The xcretion decreased irregularly after restoration an adequate diet. Thirty-four normal rats exeted 10.34 per cent (± 2.07, probable error) of the ose in twenty-four hours. Rats, fifty-seven days d, gave a response similar to those of thirty-five ys but the deficiency developed less rapidly d differences in excretion were less pronounced. nother series of older rats gave more dubious sults, with controls.

The increase in quinine excretion with B-comex deficiency following subcutaneous adminisation is compared with a previously reported ecrease following oral administration of quinine. ork is now in progress on intestinal absorption of inine in the rat during B-complex deficiency. *upported by a grant from the Samuel S. Fels und.*]

The excretion of "F_2" and its supposed relation niacin intake and metabolism. OLAF MICKELSEN troduced by Ancel Keys). *Lab. of Physiological Hygiene, Univ. of Minnesota, Minneapolis.* Najjar and co-workers (J. Clin. Invest. **21:** 263. 1942) reported that the excretion of a urinary constituent, F_2, was markedly decreased in niacin deficiency. Huff and Perlzweig (J. Biol. Chem. **150:** 483, 1943) identified this substance as N′-Methylnicotinamide and described a modified procedure for its identification. We have used both the original and the modified method in a study of the excretion of F_2 in the 24 hour urine of young men on known and fixed diets. One group received a total daily intake of 10 mg. of niacin while another received 20 mg. Over a period of 5½ months there was no significant difference in the excretion of F_2 by these 2 groups. Furthermore there was no difference in the response of F_2 excretion of these 2 groups to a test dose of 10 mg. of niacin. During a final period of 30 days when 4 of the subjects received only 0.25 mg. of niacin daily and 4 others received 10.2 mg. of niacin there was no difference in the average daily excretion of F_2. Again the responses of the two groups to test doses of 10 mg. of niacin were the same. Some of the boys on the low niacin intake showed the same relative increase in F_2 excretion following the test dose as those who had been on the higher intake. [*This work was supported in part under the terms of a contract (No. OEMcmr-27) between the Regents of the Univ. of Minnesota and the Office of Scientific Research and Development. Support from other sources will be acknowledged in final publication.*]

Storage of vitamin A in the livers of dogs fed beta-carotene or vitamin A. AGNES FAY MORGAN and LILLIAN S. BENTLEY (by invitation). *Lab. of Home Economics, Univ. of California, Berkeley.* Since the urinary excretion of vitamin A by dogs was found to be influenced by the amount and dietary source of the vitamin, as well as by the age of the dog, it was concluded that massive liver deposits were probably necessary for such excretion. Fourteen young dogs which had been depleted of vitamin A were fed known amounts of vitamin A as fish liver oil or as beta-carotene. All of these dogs were reared on purified diets containing unheated or heated casein, the latter being used to induce fatty liver. Four of the dogs fed the heated diet developed fatty livers, and one fed the unheated diet and large amounts of carotene had a cirrhotic liver.

One series of eight dogs ingested 31,000 to 65,000 I.U. of vitamin A or carotene in 28 to 68 days, and another group of six dogs, 1 million to 14 millions I.U. in 185 days. In no case was more than 6 per cent of the beta-carotene intake found deposited in the liver and kidney as vitamin A, but 18 to 56 per cent of the equivalent vitamin A ingested was found in these organs. The animals fed heated diet utilized the carotene and vitamin A as well as those on the unheated, and there was some in-

dication of increased vitamin A deposition in the fatty livers. Only the dogs found to have massive liver deposits of vitamin A had excreted the vitamin in the urine. [*Aided by a grant from Swift & Co.*]

Effect of heparin on the thrombopenia of anaphylactic and peptone shock. ROBERT K. OTA (by invitation), IVAN D. BARONOFSKY (by invitation), and ARMAND J. QUICK. *Dept. of Pharmacology, Marquette Univ. School of Medicine, Milwaukee.* In anaphylactic and in peptone shock heparin is liberated into the blood stream, histamine is released, and a marked drop of platelets occurs. In order to test whether heparin serves as a protection against anaphylactic shock, particularly against the decrease in platelets, rabbits sensitized to horse serum were given as high as 1000 units (10 mg. of Roche-Organon heparin) per kilo of body weight 10 to 60 minutes before the shocking dose was administered. The fall in platelets was not prevented: in both the heparinized and in the control animals, the drop from an average normal of 500,000 to 75,000 occurred in 5 minutes. Similar results were obtained using guinea pigs.

Heparin in large doses (500 units per kilo of body weight) did not protect dogs against peptone shock. A marked drop in platelets as well as the usual signs of shock appeared promptly after the injection of peptone. No correlation between the severity of the shock and the magnitude of the platelet decrease was noted. In rabbits the thrombopenia was in several instances the only manifestation of shock. Histamine injected intravenously produced no decrease in platelets. Splenectomized dogs were as susceptible to peptone shock as were normal animals.

There appears to be no obvious correlation between the decrease of platelets, and the production or release of heparin and histamine. Heparin does not appear to serve as a defense against shock.

The relation of phospholipid turnover to renal damage in the choline-deficient rat. JEAN M. PATTERSON (by invitation) and E. W. MCHENRY. *School of Hygiene, Univ. of Toronto.* Previous work from this laboratory indicated that renal damage, produced in young rats by a dietary deficiency of choline, was preceded by a decrease concentration of phospholipids in both liver and kidneys. This observation indicated that renal damage might be due to a lack of phospholipids needed for the development of the growing kidney.

This hypothesis has been further investigated with the aid of radioactive phosphorus (P^{32}). As previously found, the concentration of phospholipids in the kidneys and liver was markedly influenced by choline deficiency; in this experiment the average concentration was: (a) with choline, 2597 mg. and 2472 mg. per 100 grams kidney and liver respectively; (b) without choline 1358 mg. and 2135 mg. per cent. The percentage of the administered phosphorus recovered per gram of phospholipid were: (a) 7.95 and 12.8 (b) 6.09 and 8.25. The organ weights in the two groups were different and, if the recovery of radioactive phosphorus is calculated per 100 grams of tissue the percentages are (a) 20.6 and 31.4 (b) 8 and 17.5.

These results have been confirmed in two experiments with forty animals; they indicate greater turnover of phospholipid in the kidney and liver of animals given choline. A similar investigation in older rats, in which kidney damage can be produced with difficulty by choline deficiency, indicates that phospholipid turnover is much less rapid; the consequent diminished need for choline explains the difficulty of producing kidney lesions.

The excretion of thiamin, riboflavin and nicotinic acid by fasting men. WILLIAM A. PERLZWEIG, JESSE W. HUFF (by invitation) and IRMA GUE (by invitation). With the technical assistance of Evelyn Vollmer. *Dept. of Biochemistry, Duke Univ. School of Medicine, Durham.* The average daily urinary excretion of total nitrogen and of the 3 vitamins by 13 normal young men during a four day fast was as follows:

	T.N. (gm.)	B_1 (γ)	B_2 (mgm.)	N.A. (mgm.
Normal diet	12.4	216	1.46	8.1
1st fast day	9.6	126	1.45	6.2
2nd fast day	12.0	88	1.53	8.3
3rd fast day	10.7	72	1.59	8.6
4th fast day	10.3	65	1.32	7.8

The thiamin and riboflavin were estimated fluorometrically. The nicotinic acid values include the acid hydrolyzable nicotinic acid and N-methyl nicotinamide determined fluorometrically.

These data confirm our previous observations in fasting dogs (J. Nutr. 24: 295, 1943) in regard to riboflavin and nicotinic acid. It is apparent that in starvation these 2 vitamins are liberated from the tissues which contribute the urinary nitrogen. The magnitude of the riboflavin excretion suggests the probability of the liver being the chief source. The sharply diminishing excretion of thiamin probably reflects the much smaller concentration of this vitamin in the liver, and may explain the earlier susceptibility of man to depletion of B_1 compared with the other B vitamins. [*Aided by grants from The Nutrition Foundation, Inc., The John and Mary R. Markle Foundation and the Duke Univ. Research Council.*]

The oxidation potentials of cystine-cysteine and related systems. LIONEL R. RYKLAN (by invitation) and CARL L. A. SCHMIDT. *Division of Bi*

emistry, Univ. of California, Berkeley. Deter-inations of the apparent oxidation potentials, ″ under conditions of reversibility and equi-rium, have been carried out on a number of sulfide-sulfhydryl systems. The potentiometric tration method was employed and applied to all stems studied. A solution of iodine containing otassium iodide or a potassium permanganate lution was employed as oxidizing agent. In the se of cystine-cysteine the potentials of mixtures the 2 components were also measured. Iodide ns facilitate this equilibrium.

For the systems under consideration and under e experimental conditions, the following elec-ode reaction was postulated:

$$RSSR + 2\,H^+ + 2\,e \rightleftarrows 2\,RSH$$

n order to facilitate the calculation of $E^{o\prime}$ from e potentiometric titration data the following pproximate equation was used:

$$E^{o\prime}_{(RSSR-RSH)\,Pt} = E_h + 0.059\ pH - 0.059 \log \frac{x^{\frac{1}{2}}}{100 - x} - 0.059 + 0.0295 \log 2\,m$$

here E_h is the observed E.M.F. corrected to the ydrogen electrode, x is the percentage oxidation, nd m is the initial concentration of the reductant.

The following values for $E^{o\prime}$ at 25° were ob-ined: thiophenol, 0.11; thioglycollic acid, 0.27; steine, 0.27; *o*-thiocresol, 0.30; monothiolethyl-e glycol, 0.35; thiolhistidine, 0.32; ergothioneine, 36; glutathione, 0.45 volt. The corresponding quilibrium constants, are: 5.4×10^3, 1.4×10^9, 4×10^9, 1.5×10^{10}, 7.3×10^{11}, 7.0×10^{10}, 1.6×0^{12}, and 1.8×10^{15}. The values for $-\Delta F^{o\prime}_{298.1}$ xpressed in calories are: 5100, 12400, 12400, 13800, 5100, 14800, 16600, and 20800.

Studies on adenine-thiomethylpentoside. F. CHLENK and W. D. GINGRICH (by invitation). *niv. of Texas; M. D. Anderson Hospital for Can-r Research, Houston; and Dept. of Bacteriology, edical School, Galveston.* An improved method r isolation of adenine-thiomethylpentoside from east has been elaborated. It consists in extraction ith boiling water, repeated alcohol precipita-ons, phenol extraction, and crystallization. The ield is 10 to 25 mg. per cent.

The biological function of this nucleoside is as et obscure. Besides attempts to identify it with arious growth factors, experiments have been ade to establish its possible role in transmethyla-on (cf. Lipmann, F., Advances in Enzymology, **1:** , 1941) either as a methyl donator or in catalytic ncentration as a methyl vehicle.

Experiments with rat liver slices were carried t. In the reaction methionine + glycocyamine → eatine + homocysteine (Borsook, H., and Dub-off, J. W., J. Biol. Chem., **132:** 539, 1940) no significant effect resulted from the addition of adenine-thiomethylpentoside. Similarly negative results were obtained in nutritional experiments with certain bacteria. Adenine-thiomethylpentoside + homocysteine + choline failed to substitute for the methionine requirement of Photobacterium phosphoreum. The same combination failed to replace methionine for Lactobacillus casei ε and Lactobacillus arabinosus in a medium containing amino acids and vitamins. Adenine-thiomethylpentoside can, however, satisfy the purine requirement of the latter two organisms.

Physicochemistry of urea-treated proteins II. MONA SPIEGEL-ADOLF. *Dept. of Colloid Chemistry, Temple Univ. School of Medicine, Philadelphia.* Former studies (Fed. Proc. **2,** 1943) on urea-treated proteins were extended in different directions.

In a first series of experiments the effect of urea upon gelatin was tested as to the latter's protecting power for colloid gold. It could be shown that treatment with urea reduces the protective power of gelatin by approximately 50 per cent. The swelling of urea-treated gelatin is markedly decreased.

Analogous studies were made with electrolyte-free pseudoglobulin treated with urea, with and without boiling. Urea treatment of pseudoglobulin decreases the gold sol protecting power of the protein while additional boiling apparently does not affect the extent of these changes.

Urea was finally used in irradiation experiments on proteins with ultra-violet light. No formation of gold sol precipitating substances in irradiated gelatin (Bioch. J. **28:** 1201, 1934) could be detected, although urea, even after irradiation does not show any absorption within ultraviolet light range. Diluted pseudoglobulin solutions irradiated in the presence of urea show spectrographically a marked increase in density (last transmitted line 295 mμ against 240 mμ of the non-irradiated specimen). But contrary to the behaviour of pure pseudoglobulin (Bioch. J. **28:** 372, 1934) no gold sol precipitating substances appear, tentatively identified as decarboxylated amino acids. The increased light density of the irradiated material (Hausmann and Spiegel-Adolf) or a protective effect of urea for colloid gold analogous to one found against histamine precipitation may be accountable. The spectrographical changes observed, similar to changes described by Krumpel and Spiegel-Adolf, seem to preclude an interference of urea with the mechanism of light-denaturation in proteins.

The effect of parathyroid extract upon the distribution and excretion of labeled strontium. WILBUR R. TWEEDY. *Dept. of Biological Chemistry, Loyola Univ. School of Medicine, Chicago.* One hundred (Collip) units of parathyroid extract (Lilly) were administered subcutaneously to each of 6 young adult rats. One hour later a solution of

2 mgm. of $SrCl_2$, containing 2 to 3μc of radiostrontium, was administered, intraperitoneally, to each of these animals and to an equal number of their littermates. Each of 6 other young adult rats was injected with 100 units of parathyroid extract and 24 hours later these animals and an equal number of controls received the same treatment as the first group. The animals were sacrificed 24 or 48 hours after the last injection.

The average amounts of radiostrontium found in the tissues and excreta of the animals which received 100 units of parathyroid extract agreed closely with the values found for the controls.

The amounts of radiostrontium recovered from the femurs of the animals which received 200 units of parathyroid extract did not differ significantly from the controls. However, twice as much radiostrontium was found in the gastrointestinal tracts (and contents) of these animals as in their co trols, while less radiostrontium was recover from the urine or feces of the former than from t urine or feces of the latter. The kidneys of t experimental animals contained approximate thirty times as much radiostrontium as the ki neys of the controls.

A marked accumulation of radiostrontium in t kidneys of rats has been produced by injecting buffered phosphate solution (pH 6.8) followed b the injection of labeled strontium chloride. [*Aid by the Ella Sachs Plotz Foundation and by a gift parathyroid extract from Eli Lilly and Compan The author is also indebted to Prof. E. O. Lawren and Dr. Joseph G. Hamilton of the Radiation Lab ratory, Univ. of California, for supplying the radi strontium.*]

THE AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS

Abstracts of papers received from the Secretary of the Society. Since there will be no meeting in 1944 these papers are to be regarded as "read by title". For possible corrections in any of these abstracts see the next issue.

Choline esterase activity of normal and pre-eclamptic human placentas. B. E. Abreu and R. A. Woodbury. *Dept. of Pharmacology, Univ. of Georgia School of Medicine, Augusta.* Within 30 minutes of delivery normal and pre-eclamptic placentas were perfused with 3–5 liters of Ringer-Locke's solution by way of one or both of the umbilical arteries. When examination of the placentas indicated that most of the blood had been removed, bloodless portions were selected, weighed and placed in sufficient Ringer-Locke's solution to make a 10% suspension. The material was then finely minced in a Waring Blender and 1 ml. samples of the suspension were taken for analysis. Torda's modification (Proc. Soc. Exp. Biol. & Med. **31**: 398, 1942) of Glick's method for the determination of choline esterase activity was employed.

Samples of placentas were taken for water determinations and choline esterase activity calculated on the basis of dry weight. At least 3 and sometimes 6 determinations were made on 8 normal and 13 pre-eclamptic placentas. Choline esterase activity expressed as micrograms acetylcholine chloride hydrolyzed per mg. dried placenta per second were for normals 6.0 ± S.E. of 0.15 and for pre-eclamptics 9.4 ± S.E. of 0.19. Statistical evaluation by the "t" method indicates that pre-eclamptic placentas have a significantly greater choli esterase activity than those of normals (t = 4.

These data and observations that neostigmi lower arterial pressure of some pre-eclamptic p tients (see Woodbury, Abreu, Torpin and Fri these abstracts) stress the importance of acet choline in eclampsia. [*This work was aided by grant from Eli Lilly and Co.*]

Comparative effectiveness of 4,4′-diamidino sti bene and other agents in experimental leishmani sis. Hamilton H. Anderson and H. Y. Soon *Dept. of Pharmacology, Peiping Union Medic College, Peking, China.* Adler and Tchernomore (Ann. Trop. Med. Parasit. **33**: 313, 1939) report 4,4′-diamidino stilbene (Stilbamidine) activ against experimental Indian kala-azar in Syri hamsters. Subsequently (Ann. Trop. Med. Par sit., **35**: 9, 1941) they extended their observatio and found *L. infantum* infections more resistan Following a previously outlined procedure (Am. Trop. Med. **21**: 461, 1941) we gave doses of mgm/kgm. (1/10 of L D_{50}) of 4,4′-diamidino sti bene subcutaneously 3 times weekly for 5 weeks 30 Chinese hamsters (*Cricetulus griseus*) infect with a local strain of *L. donovani*. Of 26 survivo 23 were infected on completion of therapy and were not.

Six other agents were studied; 1/10 the L D_{50} dose was given 15 times in 5 weeks. Each drug was employed in 15 hamsters. The ratio of treated animals exhibiting no Leishman-Donovan bodies in splenic material to a number of survivors of therapy was: Sodium antimony thioglycolate, 7/15; m-nitrobenzoic acid, 6/15; lithium antimony thiomalate (Anthiomaline), 5/15; 3-carboxy-s-diphenyl-carbamido-4'-stilbonic acid, 5/15; sodium antimony catechol thioglycolate, 4/15; and 4,4'-diamino diphenylsulfone dextrose sulfonate (Promin), 0/14.

Drugs of known clinical value examined by this procedure gave the following results: Ureastibamine, 24 survivors of 30 treated animals exhibited no Leishman-Donovan bodies in splenic material but sub-inoculations into clean hamsters revealed that half of the survivors were infected. Neostibosan, 23 survivors of 30 treated hamsters showed no infection but sub-inoculations indicated that 13 animals were still infected. All except 1 of an untreated group of 30 hamsters remained infected throughout the period of observation.

Antibacterial properties of a sulfanilamide oxidation product. GEORG BARKAN. *Evans Memorial, Mass. Memorial Hospitals and Biochemistry Dept., Boston Univ. School of Medicine.* It has been reported previously, before this society that nascent hydrogen peroxide as formed on autoxidation of hydrazine solutions, in presence of cupric ions, oxidizes sulfanilamide to a blue-violet derivative. The assumption that on this oxidation the sulfonamide group is lost has previously been theoretically derived. It is not analytically proven, with the oxidation product isolated and purified. On the basis of elementary analysis and molecular weight determinations a tentative chemical structure of the derivative is offered. The purified material showed, alone and in presence of serum, a high antibacterial (bacteriostatic) action in vitro against streptococcus hemolyticus, staphylococcus aureus and Type I pneumococcus.

Further studies on the phase-boundary potential of acetylcholine. T. CUNLIFFE BARNES and R. BEUTNER. *Depts. of Physiology and Pharmacology, Hahnemann Medical College, Philadelphia.* The effects of temperature on the negative electrical potential of acetylcholine at an oil-saline boundary are variable and complex. Between 30°C. and 50°C. the potential fell (sample experiment: 0.05 per cent acetylcholine produced 47 mv. on cresol at 34°C. and 32 mv. at 42°C.). Between 25°C. and 10°C. the potential dropped with the temperature (42 mv. at 23°C., 37 mv. at 15°C.). Below 10°C. the potential again rose (44 mv. at 3.8°C.). At high temperatures the oil dissolves in the saline; at low temperatures there is probably a sharper phase boundary. The results may explain the reduction of the spike potential in nerve at high temperature, also the greater electrical activity of the cooled spinal cord.

At *constant temperature* the form of the potential rise after adding acetylcholine depends on the oil used. The potential rises sharply on nitrobenzene resembling a spike; on cresol the potential rises more slowly resembling the action current in slow nerves. The choline curve resembles the negative after potential Toluidine is inactive with acetylcholine and with epinephrine but triacetin gives a potential with epinephrine but not with acetylcholine (model of adrenergic nerve).

The blocking action of atropine may be explained by its reversal of an oil emulsion (shown by Bayer and Wense). The above model of the action current in nerve is supported by the demonstration of acetylcholine in sensory nerves by Lissak and Pasztor. Nachmannsohn's work on cholinesterase does not prove presence of acetylcholine nor explain origin of potential.

Chronic toxicity of an alkyl ether or cellulose methyl cellulose. ROBERT BAUER (by invitation), ARNOLD J. LEHMAN and FREDERICK F. YONKMAN. *Wayne Univ. College of Medicine, Detroit, Mich.* Methyl cellulose is a water soluble derivative of cellulose synthesized in the cold by the interaction of methyl chloride and an alkaline solution of cellulose. Purified methyl cellulose produces a clear colloidal jell when combined with water. It was by the use of this jell that the experimental diets described below were mixed, dried and ground. For chronic studies four groups of five white rats were employed, three groups of females and one of males. These animals weighed between 45 and 50 grams each at weaning. Male rats were included for the purpose of studying reproduction and effects of methyl cellulose on the second generation under similar experimental conditions. One group of females served as the control and had free access to Steenbach's whole artificial diet, and the remaining groups were placed on this basic diet in which 1.66 per cent (Dow Chemical Company), 1.66 per cent (Hercules Powder Company) and 5 per cent (Hercules) methyl cellulose had replaced carbohydrate. Each rat, then, in respective groups consumed per day of these experimental diets 0.17, 0.17 and 6.2 grams/kgm. of methyl cellulose. The experiment lasted for one hundred and eighty-four days.

Growth and food intake curves showed that the experimental groups as compared to the controls gained weight more rapidly, attained greater average weight at the conclusion of the experiment, and consumed more food per day. Gross examination of the feces of rats on the methyl cellulose diet showed a mineral oil type of stool. Pathologic examination of one rat from each group revealed no gross or microscopic effects.

It would seem, then, from this experiment that:

(1) methyl cellulose as synthesized by domestic chemical industries is nontoxic in the quantities used, (2) to secure sufficient nutrition the experimental rats must eat more bulk, and that, (3) due to the increased bulk and probably a better utilization of food by improved large bowel elimination, a more rapid growth and greater body weight is attained.

"Continuous" quinine administration in avian malaria infections. HARRY BECKMAN. *Dept. of Pharmacology, Marquette Univ. School of Medicine.* Thirty canaries were divided into 3 groups of 10 each and allowed to be bitten by *Culex pipiens* mosquitoes carrying our 3H2 strain of *Plasmodium cathemerium*. Late on the night of the fourth day plasmodia were found in the peripheral blood of all birds. During the fifth to eighth days, inclusive, one group was given 1 mg. quinine bisulfate in aqueous solution by mouth at 8 a.m., 2 p.m. and 8 p.m.; another group received the same total dosage but administered in appropriately reduced amounts at 2 hour intervals continuously throughout the 4 days; the third group was held as untreated controls. Effectiveness of the two types of treatment was determined by quantitative studies of the rates of development of the plasmodia and by daily plasmodial counts. It was found that the "continuous" type of treatment: *a*, effected an approximately 24 times greater retardation in trophozoite development that "three times daily" dosage; *b*, caused crisis to be reached on the second or third days in all birds instead of on the third, fourth, fifth or later days as in the "three times daily" treated birds.

Monocaine compared with procaine regarding vasodilatation and irritation. R. BEUTNER. *Dept. of Pharmacology, Hahnemann Medical College, Philadelphia.* Procaine, the local anesthetic generally used for injection is vasodilating (Kisch and others). An isomer of procaine, butyl-amino-ethyl-p-amido-benzoate, called "monocaine," was found to be more nearly or completely free of vasodilation, so as to require less epinephrine. Schamps and Tainter (Anesthesiology, 1942) tried to disprove this point but their observations also show that in many cases less epinephrine is needed with monocaine. Thus, e.g. the "median anesthetic" concentration of procaine tested by infra-orbital infiltration in rabbit is decreased from 0.295 per cent to 0.2 per cent if 1:50000 epinephrine is added; while for monocaine it is lowered far more, viz. from 0.35 per cent to 0.185 per cent by *only* 1:75000 epinephrine! Similarly, when testing both anesthetics by infiltration of rabbit skin, the "median anesthetic" concentration of procaine is decreased less by 1:50000 epinephrine than that of monocaine by 1:75000 epinephrine; the respective figures are, procaine: 1.5 → 0.95%, monocaine: 1.2 → 0.66%. Only in the human intracutaneous skin test the variation of potency was found to be in the same direction as the epinephrine concentration. (Abolition of epinephrine pressor effect by procaine or monocaine proves little since even ergotamine, a strong vasoconstrictor, may abolish epinephrine action.)

For testing tissue irritation by these two anesthetics 2% monocaine was instilled repeatedly on the right eye, and 4% procaine on the left eye of 13 rabbits (since monocaine is used in half the concentration of procaine). Neither of the drugs led to distinct irritation; only in one case the conjunctiva seemed slightly more reddened by procaine than by monocaine.

A theory of the absorption of iron. ELDON M. BOYD. *Dept. of Pharmacology, Queen's Univ., Kingston, Canada.* Sheline, Chaikoff, Jones and Montgomery have shown (J. Biol. Chem., 1943), that accelerated absorption of radioiron from the gastrointestinal tract does not begin immediately after acute anemia has been induced but rather a fortnight or so later when hematopoiesis is active. This suggests that the stimulus to increased iron absorption is active hematopoiesis. The chief source of iron for hematopoiesis is stored iron. Boyd, Hitsman and Perry (Rev. Canad. de Biol., 1944) found that when iron is injected intramuscularly, it is stored in many tissues of the body including the tissues of the gastrointestinal tract. Based upon these facts, the theory is advanced that iron absorption, and hence the iron content of the body, is regulated by the amount of storage iron in the tissues of the gastrointestinal tract. If gastrointestinal tissue storage iron is saturated, little or no iron is absorbed. If gastrointestinal tissue storage iron is depleted by the demands of hematopoiesis, then iron is readily absorbed from the gut until body storage iron is again saturated and an equilibrium established.

The use of thymol in clinical and experimental tuberculosis. CLYDE BROOKS and HARVEY SEARCY (by invitation). *School of Medicine, Louisiana State Univ., New Orleans.* Ralph McBurney, Harvey Searcy, and Louise Cason were the first to perform experiments on the effect of thymol on experimental tuberculosis in the guinea pig. Their publication is now in progress.

Searcy, McBurney, and Rowe (J. Ala. Med. Assn. 2: 217, 1942) were first to report the treatment of human cases of tuberculosis of the lungs with thymol.

The present paper is a further report on the use of thymol both in experimental tuberculosis in the guinea pig, and also on human cases of tuberculosis of the lungs.

A preliminary report of this work was read by title before the Boston sessions of the American Society for Pharmacology and Experimental

Therapeutics (Brooks and Searcy, Fed. Proc. 1: Part II: 145, 1942).

Two series of guinea pigs have been studied, using adequate controls, which show:

Thymol treated animals did not all die; but all controls died. Thymol treated animals did not lose as much weight as did the controls. Thymol treated animals did not have as much tuberculosis as shown at autopsy, as did the controls. These results indicate that the thymol exerts a restrictive effect on tuberculosis in the guinea pig.

One hundred and seven human cases of tuberculosis of the lungs have been treated with thymol, with controls of similar but untreated cases. The results thus far are encouraging, and will be reported in detail in due time.

Anesthetic activity of the cis-trans isomers of trichloroethylidene glycerol. THOMAS C. BUTLER. *Dept. of Pharmacology, Vanderbilt Univ. School of Medicine, Nashville, Tenn.* By benzoylation, separation of the crystalline benzoates, and hydrolysis of the benzoates, trichloroethylidene glycerol (2-(trichloromethyl)-1,3-dioxolane-4-methanol) has been separated into the component *cis-trans* isomers (each a racemic modification). Their melting ranges are −50 to −35 and +19 to +28°C., respectively. Both are soluble to the extent of about 3 grams per 100 cc. of water. The two isomers have been studied in comparison with tribromoethanol with respect to their anesthetic and lethal effects in mice following intravenous and intraperitoneal injection. Both isomeric forms of trichloroethylidene glycerol produce a quiet anesthesia of brief duration and they are nearly equal in activity. They are little less active both by the intravenous and by the intraperitoneal route than is tribromoethanol, but their lethal doses by both routes are notably higher.

Relative acute toxicity of some organic compounds following oral administration and skin application. HERBERT O. CALVERY, JOHN H. DRAIZE and GEOFFREY WOODARD (by invitation). *Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington, D. C.* In comparing acute toxicity by oral administration and skin application to rabbits, diethylene glycol-monobutyl-ether-acetate (I), diethylene glycol-monoethyl-ether (II), diethylene glycol (III), dimethyl phthalate (IV), 2-ethyl-11,3 hexanediol (V), isobornyl thiocyano acetate (VI), beta thiocyano ethyl esters of C_{10-18} fatty acids (VII), and beta-butoxy-beta-thiocyano-diethyl ether (VIII) were considerably more toxic orally.

a,a′-dimethyl-α-carbobutoxydihydro- gamma-pyrone (IX), 2-ethyl butanol (X), and 2-methyl-2,4-pentanediol (XI) were of the same order of toxicity by either route of administration.

Dibutyl oxalate (XII) appears somewhat more toxic by topical application.

For a number of the above compounds acute oral toxicities have also been determined using rats, mice, guinea pigs and chicks.

I and II are absorbed as readily by the intact as the abraded skin, whereas III and XI are absorbed much more readily by the abraded skin.

The increasing order of oral toxicity for the compounds is IX, XI, IV, III, II, I, V, X, XII, VII, VI, and VIII, whereas following topical application the order is IV, V, III, VI, VII, II, I, IX, XI, X, XII and VIII. It is impossible to predict toxicity by skin application from oral data and vice versa.

Comparative assays of various digitalis materials by the U.S.P. cat method and the human method. MCKEEN CATTELL and HARRY GOLD. *Dept. of Pharmacology, Cornell Univ. Medical College, New York, N. Y.* The data in the accompanying table are illustrations of the limitations of the cat method as a measure of potency of digitalis materials for oral administration in man. The U.S.P. official technique was employed in the case of the cat method and the technique described in the J. Pharm. and Exper. Therap., **75:** 196, 1942 for the human method.

Preparation	Potency in terms of USP Digitalis Reference Standard 1942		Potency by human method in percentage of potency by cat method
	Cat method (intravenous)	Human method (oral)	
1. Digitaline Nativelle	180	1000	555
2. Gitalin	100	181	181
3. Indian Urginin	193	99	51
4. Lanatoside C	300	±150	50
5. Digitalis Leaf	1.05	1.00	95
6. Digitalis Tablets	1.04	0.90	87
7. Digitalis Tablets	1.17	1.13	97
8. H. A. #9 Leaf	1.32	1.15	87
9. Digitalis Leaf	1.60	0.94	59
10. Digitalis Leaf	1.84	1.03	56
11. Tincture Digitalis	1.40	1.07	76
12. USP XI Reference Digitalis	1.67	1.33	80

It may be seen that while the cat and the human assays sometimes give fairly similar results, there are frequent discrepancies. Some specimens of digitalis were nearly one-half as potent by the human as by the cat method. The greatest discrepancies appear in the case of purified materials. Digitaline Nativelle was more than five times as potent by the human as by the cat method, and Gitalin nearly twice as potent. Urginin and Lanatoside C, on the other hand, were only about one-half as potent by the human as by the cat method. These discrepancies are undoubtedly due chiefly to differences in absorption.

The results indicate that a U.S.P. unit (intravenous cat method) may show considerable variation

in its effect by oral administration in man in the case of Digitalis Leaf and the Tincture, and that in the case of purified digitalis materials is without meaning. In the present state of our knowledge, therefore, the human method of assay is essential to insure uniformity of digitalis materials by oral administration in man.

Studies on synthetic curare-like compounds; actions and toxicity of some new quinine derivatives. HAROLD F. CHASE (by invitation) ARNOLD J. LEHMAN, KATER DONELSON (by invitation) and PAUL GRADOLPH (by invitation). *Wayne Univ. College of Medicine, Detroit, Mich.* A series of seven new quinine derivatives (J. Pharm. and Exper. Therap. **75**: 265–269, 1942) were examined for their curare-like action. The compounds investigated were quinine n-propyl bromide, quinine isoamyl chloride, quinine n-amyl bromide, quinine hexyl bromide, quinine isopropyl chloride, quinine n-propyl chloride, and quinine n-butyl chloride. All of these substances, with the exception of quinine isopropyl chloride produced a curare-like paralysis in frogs in doses of less than 100 mg/kg. when administered by ventral lymph sac.

LD_{50} values, signifying complete paralysis, including paralysis of respiration, were determined by intravenous injection into rats, rabbits and dogs. The n-propyl bromide and chloride and the n-butyl chloride derivatives were most potent. The Thomas and Franke technique was employed with dogs to study further the curarizing power of the agents in the series. All compounds showed paralysis of the peripheral respiratory neuro-muscular mechanism without central depression in doses which ranged from 50% to 100% of the canine LD_{50}. Quinine n-propyl bromide had the widest margin of safety with its LD_{50} in dogs established at 5.9 mg/kg. and the effective paralytic dose ranging from 2.5 to 5.0 mg/kg. Doses of 5.0 mg/kg. gave 80% protection against metrazol convulsions in dogs.

Thus, on the basis of preliminary experiments, quinine n-propyl bromide, which was the most effective member of the present series, is slightly less potent than quinine ethochloride (J. Pharm. and Exper. Therap. **75**: 270–276, 1942) which gave complete protection from metrazol convulsions in a dose less than its LD_{50}.

Variation in reproductive phenomena by caffeine. RALPH H. CHENEY. *Dept. of Biology, Long Island Univ., Brooklyn, N.Y.* Preliminary investigations regarding the effect of caffeine upon reproductive phenomena indicate respiratory effects on the fertilized ova. The influence of caffeine on the fecundity and normalcy of the progency constitutes a separate phase of the work. The eggs and sperm of Arbacia punctulata were used as the experimental material for respiratory data. Measurements were made by means of the Warburg microrespirometer. White rats were the source of data on the fecundity and normalcy studies.

Respiration: Caffeine-in-sea-water percentage varied from 0.002% to 2.0%. Temperature was controlled at 25°C, total volume in each flask was 2 c.c., and the readings recorded on oxygen consumption were made over a three hour period. The time relationship curve expressed in cu. mm. of oxygen consumed in non-caffeinized controls was compared with the caffeinized experimentals. Changes of less than 10% were not considered significant. Concentrations of caffeine-in-sea-water equivalent to 0.1% or above produced inhibition of oxygen consumption. Cleavage rates are also arrested in high concentrations.

Fecundity: The rat colony fecundity studies are a part of a five year investigation. Diet control maintained parallel conditions between experimentals and controls with the exception of the caffeine intake. Different concentrations were supplied to the separate groups within the colony. The experimental group received only water with caffeine from the weaning period throughout their life. Data is incomplete, but there is some evidence of reduced fecundity. Final substantiation remains to be determined.

A method for determining the length of action of barbiturates. VERSA V. COLE and H. R. HULPIEU. *Dept. of Biochemistry and Pharmacology, Indiana Univ. School of Medicine, Indianapolis.* Previous work on convulsants by one of us indicated the possibility for the development of a test method for the length of action of barbiturates. A method has been developed on 4 barbiturates (sodium pentobarbital, sodium amytal, sodium barbital and sodium phenobarbital). For the convulsant strychnine was given 3 mgm. per kgm. by intraperitoneal injection. This dose of strychnine killed 70 per cent of male rats weighing from 65 to 8[illegible] grams. A dose of each barbiturate was determined which would protect at least 9 of 10 rats against death from strychnine when the barbiturate was given one hour before. The same dose of each barbiturate was given one hour before. The same dose of each barbiturate given 2 hours before strychnine to 10 rats each, served to differentiate between the medium and long acting barbiturates. The deaths from strychnine after sodium barbital and sodium phenobarbital are the same at 2 hours as at one hour. Two hours after sodium amytal and sodium pentobarbital, 5 of 10 died from strychnine. To differentiate between sodium barbital and sodium phenobarbital, it was necessary to use 20 rats each at 48 hours after the barbiturates. Three rats out of 20 were killed by strychnine 48 hours after sodium phenobarbital and 11 rats out of 20 were killed by strychnine 48 hours after sodium barbital.

These results are statistically significant and are

not related to the dose of barbiturate or to the degree of anaesthesia. This method of determination has proved impractical on short acting compounds. It should be useful in differentiating medium and long acting barbiturates, if the toxicity is not too high.

A simple demonstration of the Ritter-Valli-Rosenthal-Heidenhain law. HELEN C. COOMBS and F. H. PIKE (by invitation) *Dept. of Hygiene, Brooklyn College and Columbia Univ.* Valli, about 1792, showed that when a nerve is divided anatomically the proximal end of the severed portion becomes inexcitable at a time when more distal portions closer to the muscle remain excitable. This was confirmed a few years later by Ritter. A half century later Rosenthal and Heidenhain showed that a wave of increased excitability begins at the proximal end of the severed portion of the nerve and passes out to the periphery.

If a sciatic-gastrocnemius preparation is excised and the excised muscle drawn under the intact sciatic nerve of the frog, the nerve of the excised preparation may be stimulated and the excised muscle made to contract while remaining in contact with the uninjured sciatic of the other leg. The gastrocnemius of the uninjured side will not contract. Stimulation may be carried out repeatedly for half an hour or more without causing any contraction of the uninjured side. If, however, the intact sciatic be cut, and the end remains in contact with the excised muscle, the gastrocnemius of the previously uninjured side will contract. We would make the suggestion that this method of using an uninjured nerve in continuity affords a biological means of determining the effects of various agents upon the excitability of nerve without introducing the complications inevitable to any anatomical injury.

The pressor action in the intact dog of 2-naphthyl-(1′)-methyl-imidazoline-hydrochloride (Privine). BRADFORD N. CRAVER and HAROLD F. CHASE (by invitation) and FREDRICK F. YONKMAN. *Wayne Univ. College of Medicine, Detroit, Mich.* Dogs were anesthetized with urethane, ether or sodium pentobarbital. The blood pressure was continuously recorded with a carotid cannula and mercury manometer and the respiration with a Mendenhall pleural cannula. The minimally effective intravenous dose of Privine (Ciba) for the dog ranged between 1 and 5 micrograms per kilogram. Five micrograms of Privine per kilogram gave roughly ⅓ the response of an equal dose of epinephrine. Larger doses of Privine compared less favorably with epinephrine although their duration of action was often twice or more that of epinephrine. No dose of Privine gave as high a response as could be elicited by a suitable dose of epinephrine. The therapeutic ratio for Privine was high since 1 mg/kg. was not lethal. Tachyphylaxis with Privine was slight and inconstant for doses up to 40 micrograms per kilogram and was exhibited only by dogs anesthetized with sodium pentobarbital. Privine usually inhibited the respiration of dogs under pentobarbital, inconstantly inhibited that of dogs under urethane and stimulated that of dogs under ether. Yohimbine and ethyl yohimbine markedly decreased the effectiveness of Privine but never reversed its action. Cocaine occasionally but only slightly potentiated the action of Privine. Privine inconstantly potentiated the action of epinephrine. Privine seemed to be very poorly absorbed across mucous membranes. Large doses (up to 50 mgs.) given rectally or gastrically did not alter the blood pressure or respiration. Relatively large doses of Privine in the ileum occasionally produced slight changes in blood pressure and respiration, as they did at times when administered nasally. Nasally, however, therapeutic doses had no systemic effect in these experiments.

Methods for the study of skin absorption. J. H. DRAIZE and E. P. LAUG (by invitation). *Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington, D. C.* Methods and procedures were devised for acute, short subacute and more prolonged subacute toxicity studies of substances applied topically to animals. Although animal skin differs from human skin, the rabbit for various reasons is the animal of choice.

For acute toxicity tests, rabbits weighing 2.5–3.0 kg. are clipped free of hair around the body trunks; both intact and abraded (epidermal incisions spaced 2 cm. longitudinally over the area of exposure) skin are exposed. The dose is held in contact with an area of skin 8 cm. wide around the trunk by a bell-shaped rubber cuff fitted snugly at the ends. During the 24-hour period of exposure animals are immobilized in a special holder (Laug, E. P., J. Lab. and Clin. Med., in press). From the mortality ratios at given dose levels the LD_{50} is calculated.

The techniques involved in the short subacute and more prolonged subacute experiments are essentially similar. The former experiments are designed to run 3 weeks, whereas the latter run 3 months. Dosage levels in the short subacute experiments are higher. Body weight curves, symptoms of toxicity or dysfunction, hematology, chemical tests on blood and urine, histopathology, and kidney and liver function tests are made.

The subacute experiments are important because (1) systemic effects of repeated small doses on the animal may be observed, (2) systemic effects may differ seriously from those following acute exposure, (3) effects of repeated application to the skin may be studied (progressive deteriora-

tion as a barrier) and (4) the cumulative effects finally manifested by a serious dermatitis.

Diffusion respiration in the dog under pentothal sodium. W. B. DRAPER and R. W. WHITEHEAD. *Dept. of Physiology and Pharmacology, Univ. of Colorado, Denver.* Under certain conditions, the anesthetized dog in respiratory arrest can obtain sufficient oxygen for metabolic requirements through diffusion alone. The necessary conditions are the replacement of the nitrogen in the respiratory tract and surrounding atmosphere with oxygen, and an adequate circulation. Under these conditions, the oxygen uptake from a spirometer by dogs in respiratory arrest induced by pentothal may be more than 80% of the amount taken up during spontaneous respiration. The uptake of oxygen in respiratory arrest is due to the affinity of the reduced hemoglobin in transit through the alveolar capillaries for the oxygen within the alveolar spaces. As oxygen is removed from the lungs by the blood, there is diffusion of an equivalent amount inwards from the spirometer. The suction thus exerted is considerable and will cause collapse of the lungs if diffusion of oxygen from the spirometer into the lungs is prevented by seizure of the spirometer bell. The diffusion outwards of CO_2 is slower than the diffusion inwards of oxygen, and the alveolar CO_2 may reach 30% before death. Dogs in an oxygen chamber may be held in respiratory arrest with pentothal for more than an hour and yet spontaneously recover without the aid of any sort of artificial respiration. More than sixty dogs have been resuscitated from gross overdosage with pentothal through the use of diffusion respiration alone. The presence of substantial amounts of nitrogen in the respiratory tract or surrounding atmosphere impedes the inward diffusion of oxygen and prevents effective diffusion respiration.

The action of barbiturates on the motility of the cat's stomach and intestines. N. B. DREYER, L. RAY (by invitation) and V. LARSON (by invitation). *Dept. of Physiology and Pharmacology, L. I. College of Medicine, Brooklyn, N. Y.* Observations were carried out on the stomach and intestines in situ. The cats were either decerebrated or anesthetized with chloralose. Sodium salts of the barbiturates were injected intravenously in all cases. Dosages varied from fractions of a milligram to the usual anesthetic dose.

Small doses caused an increase in motility without a change in tonus. Thus, 1 mg/kg of sodium amytal produced an increase in motility lasting up to five minutes, followed by a return to normal. Doses of 4 mg/kg of sodium amytal raised the tonus and increased the height of contractions. As the dosage increased there was a still further rise in tonus and motility of longer duration than with the smaller doses. There appeared to be a rough parallelism between hypnotic activity of the barbiturates and stimulating effect on the intestine.

Anesthetic doses produced a transitory fall in tonus and diminished motility lasting for several minutes. This was followed by a period of increased motility and heightened tonus. If artificial respiration was carried out during the injection of anesthetic doses, the depression of tonus and motility was slight or absent.

Section of both vagi and splanchnic nerves does not alter these responses, showing that they are not of central origin. Administration of atropine (1 mg/kg) also does not abolish these responses.

The thio-barbiturates on injection produce a temporary loss in tonus and diminished motility followed by a return to normal in five to ten minutes.

The effect of stimulation of the vagus nerve on tonus of the intestine of the cat. N. B. DREYER, L. RAY (by invitation) and V. LARSON (by invitation). *Dept. of Physiology and Pharmacology, L. I. College of Medicine, Brooklyn, N. Y.* The statement has been made that the effect of vagal stimulation on the tonus of the intestine depends on the preëxisting tonus of the intestine. When tonus is high vagal stimulation diminishes it; when tonus is low vagal stimulation causes an increase. Experiments carried out in this laboratory have shown that vagal stimulation always increases tonus whether tonus be high or low. To test the above hypothesis the following experiments were carried out. Movements of the intestine in situ (duodenum, jejunum, ileum, and proximal colon) were recorded in cats. The cats were either decerebrated or under chloralose anesthesia. The left vagus was sectioned in the neck for stimulation. Stimulation for a period of 30 seconds with a faradic current of submaximal intensity in the intestine with nerve supply intact produced an increase in tonus and motility. Increased tonus of the intestine was produced by sectioning of the sympathetic nerve supply. Vagal stimulation in this case produced a still further rise in tonus. Injection of morphine sulfate (1 mg/kg) causes an increase in intestinal tonus. Vagal stimulation, following morphine, causes a further rise in tonus.

Lowering the tonus by the intravenous injection of 2.5% $MgCl_2$ (1 cc/kg) or of papaverine hydrochloride (1 mg/kg), followed by vagal stimulation, results in an increased tonus.

These results indicate that vagal stimulation gives the same type of response on the intestine regardless of the previous state of tonus.

Cholinesterase activity in normal and thiouracil treated rats. SYDNEY ELLIS and MARY A. ROOT (introduced by Otto Krayer). *Dept. of Pharmacology, Harvard Medical School, Boston.* When male and female adult rats were supplied thiouracil (1:1,000) for about three months in their

drinking water in order to suppress thyroid function (Astwood, E. B., J. Pharmacol. and Exper. Therap. **78**: 79, 1943), the cholinesterase activities of the sera and homogenized whole livers of these animals were found to be about twice as high as those of control animals of the respective sexes. In both the control and treated groups the sera and livers of female rats had higher cholinesterase activities than those of the males. The homogenized cerebral hemispheres of treated and untreated animals of both sexes fell within the same rather narrow range of cholinesterase activity.

The increases in serum and liver cholinesterase are not the result of a direct activation of cholinesterase by thiouracil, since, *in vitro*, added thiouracil in concentrations between 1:1,000,000 to 1:5,000 did not activate the enzyme (1:2,000 caused slight inhibition).

Our determinations were done by the Warburg constant volume manometric method. The sera were diluted 1:10 or 1:20 with bicarbonate-salt solution; the livers, 1:20 or 1:80; and the brain, 1:20. The substrate was acetylcholine bromide in a final concentration of 0.8 M in the reaction mixture. This approaches the maximal substrate concentration for the serum and liver enzymes. At lower concentrations the activities of serum and liver cholinesterase were diminished, whereas that of the brain was much greater. Furthermore, the brain enzyme hydrolyzed acetyl-β-methylcholine as rapidly as acetylcholine, while on the former the liver and serum had only a negligible action. [*This work was done under the auspices of the University Committee on Pharmacotherapy.*]

Relative effects of *d*- and *l*-amphetamine on metabolic rate in man. G. A. Emerson. *West Virginia Univ. School of Medicine.* O_2-consumption and pulse rate were determined 30, 60, 120 and 180 minutes after oral administration of 20 mgm. of the sulfates of the optical isomers of benzedrine to 11 young adults. Technics used were the same as in a previous study (W. Va. Med. J. **37**: 74, 1941) of *dl*-amphetamine. All subjects received both forms, with an interval of 1 week between tests; *d*-amphetamine was given initially in 5 and *l*- in 6. The average maximum increase in O_2-consumption during the 3-hour period, above the basal rate determined immediately before administration of either agent, was 11.5% for *d*- and 5.5% for *l*-amphetamine. A decrease occurred in 7 receiving *l*-amphetamine (av. for the whole group, −2.5%) and in 3 receiving *d*-amphetamine (av. for the whole group, −1.5%). Only 1 subject showed an increase of > 10% after *l*-amphetamine, while only 3 showed an increase of < 10% after the *d*-isomer. However, the largest single increase (22%) was found with the *l*-form and the largest single decrease (10%) with the *d*-form. Changes in pulse rate were irregular. In view of the larger av. increase noted after *dl*-amphetamine (15.7%) than with either optical form, synergy of the latter must occur.

The circulatory action of a number of new phenylpropylamines. Edwin J. Fellows. *Temple Univ. School of Medicine, Philadelphia, Pa.* The intravenous circulatory activity of the following propylamines was compared with that of corresponding phenethylamine derivatives and epinephrine in atropinized dogs anesthetized with nembutal: dihydroxy-γ-ketophenylpropylamine (I); hydroxy-γ-ketophenylpropylamine (II); hydroxy- phenyl-n-propanolamine (III); γ-ketophenylpropylamine (IV), phenyl- n- propanolamine(V); methoxy-γ-ketophenylpropylamine (VI); dimethoxy-γ-ketophenylpropylamine (VII). These derivatives all were found to exhibit pressor activity. The above listing is in the order of their decreasing pressor effectiveness. The most active compound (1) manigested 1/100–1/200 and the least active agent (VII) possessed < 1/5000 the activity of epinephrine.

Benzedrine antagonism to certain effects of furfuryl trimethyl ammonium iodide (furmethide). Edwin J. Fellows and Raymond W. Cunningham. *Temple Univ. School of Medicine, Philadelphia, Pa.* Subcutaneous or intravenous injection of furmethide in unanesthetized dogs results in marked salivation, defecation and vomiting. The intensity as well as duration of these effects are diminished by subcutaneous or intravenous injection of benzedrine. The lethal effect of benzedrine and furmethide appears to be additive and not antagonistic because in rats one third the intravenous LD_{50} of furmethide plus LD_{50} doses of benzedrine intravenously caused death in all animals injected.

The application of certain sulfathiazole preparations to the nasal mucosa of rabbits. Edwin J. Fellows, Raymond W. Cunningham and Lawrence W. Smith. *Temple Univ. School of Medicine, Philadelphia, Pa.* Despite their high alkalinity, solutions of sodium sulfathiazole have been used extensively in the nose and paranasal sinuses. Two reports have been made that inflammation always was detectable in rabbits after intranasal application of 5% sodium sulfathiazole solution and subsequent microscopic study of the sections from these animals. A 2.5% solution of sodium sulfathiazole with 0.125% desoxyephedrine and a 5% suspension of microform sulfathiazole with 1.0% paredrine hydrobromide recently have been introduced. The effect of these two preparations on nasal mucosa has not been reported. The present studies therefore were carried out to determine the effect of intranasal application of the following:

I. 2.5% Microsulfathiazole suspension plus 1.0% paredrine hydrobromide.

II. 5.0% Microsulfathiazole suspension plus 1.0% paredrine hydrobromide.

III. 2.5% Sodium sulfathiazole solution.
IV. 2.5% Sodium sulfathiazole solution plus 0.125% desoxyephedrine.

A total of sixteen rabbits was used and each of the above preparations tested on a group of 4 animals. After a ten day period during which 0.6 cc. quantities were applied to each nostril 3 times daily, the animals were sacrificed and microscopic examinations of the sections made by one of us (L. W. S.) without knowledge of the nature of the solutions applied. Little or no change occurred in the nasal mucosa of the rabbits treated with either I or II. There was however, definite evidence of inflammation in the two series in which III and IV were employed although the severe necrotizing changes reported by other authors for 5% sodium sulfathiazole solutions were not noted.

Anticonvulsant properties of diethylsuccinyl urea. J. K. FINNEGAN. *West Virginia Univ. School of Medicine.* Diethylsuccinyl urea, hitherto undescribed, was synthesized by the method of Michael (J. prakt. Chem. **35**: 449, 1887) and its toxicity, hypnotic potency and anticonvulsant properties were studied in mice. Intraperitoneal doses of 100 mgm/kgm. are tolerated but no evidence of hypnosis is seen until higher doses within the lethal range are reached. Upon oral administration, toxicity is approximately the same as by the intraperitoneal route, although the larger doses produce hypnosis followed by recovery in a small proportion of animals. When lethal doses of diethylsuccinyl urea and a certain convulsant dose of picrotoxin are simultaneously administered intraperitoneally, all mice so treated are protected from convulsions but later die of respiratory failure. These results are of interest in regard to the mechanism of action of hydantoinates and barbiturates vs. convulsants. Further study of diethylsuccinyl urea (succinal) and other di-substituted succinyl ureas is in progress. [*These experiments were done in the Dept. of Pharmacology, Univ. of California Medical School.*]

Methyl cellulose as a solidifying agent for semi-solid media. J. K. FINNEGAN (by invitation) and G. A. EMERSON. *West Virginia Univ. School of Medicine.* In testing its stability during growth of various clostridia, it was noted that the aqueous gel formed by this ether is a suitable substitute for agar gel in semi-solid media of the type described by Spray (J. Bact. **27**: 32, 1934). Twelve representative media were prepared with varying contents of methyl cellulose. A content of 3-8% methyl cellulose is satisfactory. Methyl cellulose media cannot be made in bulk and tubed in the usual way; a weighed amount of the solid must be added to each tube. The ether withstands autoclaving well although it is precipitated on heating and redissolves upon cooling. A brilliantly clear semi-solid gel results with the recommended concentrations. Higher concentrations do not produce a gel suitable for plating, due to syneresis.

The chronic toxicity of quinacrine (Atabrine). O. G. FITZHUGH and A. A. NELSON (by invitation). *Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington, D. C.* Albino rats at the age of three weeks were placed on diets containing quinacrine (Atabrine) hydrochloride in concentrations of 100, 200, 400 and 800 ppm. A relatively low protein (11%) diet and a high protein (35%) diet were used with each concentration of quinacrine.

Toxic symptoms were produced at all concentrations of quinacrine. At the 100 ppm. level the symptoms consisted of a slight retardation of growth and an uneven coat. At the higher levels the symptoms became progressively more severe. The 800 ppm. is the only dosage level which has significantly affected the mortality rate up to the present time. The animals on the low protein diet at this level lived an average of 96 days. Those on the high protein diet survived longer; however, there is only one of the original 18 living at 11 months. Blood studies showed a marked leukocytosis in the groups on 800 ppm. and a slight leukocytosis in the groups on 400 ppm. Grossly the rats on the higher dosages of quinacrine have shown a severe necrosis and varying degrees of hyperplasia of the liver, generalized yellow staining of the viscera, peritoneal adhesions, relative enlargement of the spleen, atrophy of the testis, and other moderate changes due to inanition. Microscopically the outstanding changes have been necrosis of the liver, focal necrosis of the myocardium and of voluntary muscles, hyperplasia of the bone marrow, and the presence of small basophilic granules and of foamy macrophages in several locations.

Further observations on the reliability of the human method for the assay of digitalis materials. HARRY GOLD. *Dept. of Pharmacology, Cornell Univ. Medical College, New York, N. Y.* A method for the assay of digitalis materials on humans was published July, 1942. The unknown specimen was administered to a group of subjects which had previously been calibrated with the Standard Reference Digitalis Powder and found sensitive to about 25% differences in dosage. The criterion was a change in the RT-T segment of the electrocardiogram. The effects were ranked by the blind test. Studies have been extended to explore further the reliability of the method.

Each of three cardiologists previously unfamiliar with the method, independently ranked the tracings obtained in the assay of one specimen of digitalis (HA9) which had been tested on seven calibrated patients. The results were as follows: 100 mgm. of the unknown had the effect of 115.7 mg. of the U.S.P. XII Reference Standard in the

case of Dr. En, 115.4 in the case of Dr. Cd, and 115.2 in the case of Dr. Pe.

The reliability of the method was tested in another way by assaying the Standard Reference Powder as an unknown against itself. Eighteen calibrated subjects were divided into three equal groups, and each group of six was used for a separate assay. The ranking of the tracings was made by one of us (H. G.) and independently by the electrocardiographic assistant (J. O.). In these assays 100 mg. of the unknown (in this case U.S.P. XII Reference Powder) had the following potencies in mg. of U.S.P. XII Reference Powder: 104.5 (100.4) mg.; 102.2 (100.4) mg.; 107.7 (108.0) mg. The values in parentheses are those of the electrocardiographic assistant.

These results lend strong support to the conclusion reached in the original description of the method that if appropriately calibrated patients are employed, digitalis materials may be assayed against the Standard by oral administration in man with a high degree of reliability.

Further studies on the central nervous system action of benzimidazole HCl. LOUIS GOODMAN and NANCY HART (by invitation). *Dept. of Pharmacology, Univ. of Vermont College of Medicine, Burlington.* Detailed analysis has been made of the previously reported selective depressant action of benzimidazole on the cerebrospinal axis. Lower spinal segments are first to exhibit depression. After suitable parenteral doses (300 mgm/kgm.), the ascending depression successively involves higher levels. Respiration remains adequate throughout a wide dose range, despite loss of skeletal muscle tone. Extreme muscular flaccidity associated with exaggerated deep reflexes (and at times with clonus) is a unique neurological feature seen in both intact and spinal animals. In acute decorticate cats, "sham rage," righting reflexes, and extensor rigidity are abolished by moderate doses. In decerebrate animals, extensor rigidity and tonic neck and labyrinthine reflexes disappear. In acute and chronic spinal cats, flexor (nociceptive) reflexes are abolished, myotatic (stretch) reflexes enhanced, and skeletal muscle tone greatly diminished. Analysis of spinal cord action potentials (courtesy Drs. A. Wikler and P. C. Lloyd) indicates that benzimidazole augments two-neurone arc transmission and depresses multineuronal arcs. Obtundation of nociceptive reflexes in animals permits surgical abdominal procedures. Whether true analgesia exists is not yet known. Benzimidazole does not alter the E.E.G. and is useful for immobilizing laboratory animals for electroencephalography. Coramine specifically antagonizes benzimidazole, differing from other analeptics in this regard. Benzimidazole prevents electroshock convulsions in cats and monkeys (Offner apparatus). In a patient with Little's disease given a minimally effective dose of benzimidazole HCl intravenously (assistance of Drs. Wesley Bourne and M. Digby Leigh gratefully acknowledged), the outstanding clinical effect was temporary relaxation of skeletal muscular spasm. [*This investigation has been made with the assistance of a grant from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association.*]

The diuretic action of benzimidazole. LOUIS GOODMAN and NANCY HART (by invitation). *Dept. of Pharmacology, Univ. of Vermont College of Medicine, Burlington.* Rats given benzimidazole HCl intraperitoneally (200 mgm/kgm. daily) uniformly exhibit marked increases in water consumption and urine output. Polyuria is detectable within 3 days, reaches a peak plateau after 2 weeks, and persists as long as benzimidazole is administered (120 days). Despite a 10 to 20-fold increase in urinary volume, chloride reabsorption is only minimally impaired. Average control values and data on best performers per 24 hr. period based on 100 Gm body weight are as follows:

	H_2O consumption (cc.)	Urine volume (cc.)	Urinary chloride (mEq)
Control	10	<2	0.23
Benzimidazole	40	30	0.53

Analysis reveals that polyuria results from polydipsia, that the diuresis is not "osmotic" in character, that hypothalamic-hypophyseal mechanisms are not concerned, and that the polyuria is uninfluenced by large repeated doses of posterior pituitary (500 milliunits/100 Gm). In vitro and in vivo experiments indicate no *direct* benzimidazole—posterior pituitary antagonism.

Despite continued polyuria and polydipsia, young rats grow normally, chloride balance is maintained, and no histopathologic changes occur in the hypothalamus, postpituitary, kidneys, or other organs. The marked polyuria apparently results from a specific inhibition by benzimidazole of renal tubular reabsorption of water *per se*. If this is true, analysis of benzimidazole diuresis has heuristic value. Further investigation of the effect of benzimidazole on renal function and water and electrolyte metabolism are in progress. Congeners, minimal dosage and other species are being studied. [*This investigation has been made with the assistance of a grant from The Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association.*]

A rapid method for the estimation of penicillin. A. GOTH (by invitation) and M. T. BUSH. *Dept. of Pharmacology, Vanderbilt Medical School, Nashville, Tenn.* Actively multiplying Staphylococcus aureus cultures produce nitrite from

nitrate. It was found that penicillin decreases the production of nitrite. This observation is the basis of a rapid method for the estimation of penicillin and other antibiotic substances (flavicin) which inhibit the growth of Staphylococcus aureus.

A twenty-four hour culture of Staphylococcus aureus is suspended in the porportion of 1:4 in a culture medium which contains: peptone 2.0%, NaCl 0.6%, $NaNO_2$ 0.02% and *p*-amino-benzoic acid 0.05%. This suspension is cooled on ice for 15 minutes. A standard solution of penicillin and the unknown solutions are diluted to contain 0.5 to 1.5 Oxford Units per cc. and 1.0 cc. portions are pipetted into 50 cc. Erlenmeyer flasks. Five cc. portions of the ice cold bacterial suspension are added. The flasks are incubated for 90 minutes at 37°C. They are removed from the incubator and placed in ice water. The concentration of nitrite is then determined. The determination of nitrite is based on the diazotization of the *p*-amino-benzoic acid present in the cultures and the coupling of this diazonium salt with N-(1-naphthyl) - ethylenediamine - dihydrochloride. Since there is an excess of *p*-amino-benzoic acid present the intensity of the color depends on the amount of nitrite produced by the Staphylococcus aureus suspension. The controls without penicillin and the solutions which contain 0.5, 1, and 1.5 Units of the standard solution of penicillin give a curve from which the concentration of penicillin in the unknowns can be read in Oxford Units.

A study of the toxiciological and pharmacological actions of sec-butyl ethyl barbituric acid (butisol). CHARLES M. GRUBER, FRED W. ELLIS (by invitation) and GOLDIE FREEDMAN (by invitation). *Dept. of Pharmacology, Jefferson Medical College, Philadelphia.* Although the toxicological and pharmacological actions of sec-butyl ethyl barbituric acid (butisol) are still undetermined, it is being used in clinical medicine. So far the results of only one investigation have appeared in the literature, an article published by Fitch and Tatum in 1932, in which only rabbits and rats were employed. In the series of experiments here reported we used dogs, cats, rabbits, albino rats, white mice, terrapin and frogs.

The intravenous LD_{50} was found to be 91 mg./Kg. for rabbits and 90 mg./Kg. for dogs. The intraperitoneal LD_{50} for white mice was 247 mg./Kg. and for albino rats 66 mg./Kg. A comparison of the toxicity of this chemical and of other barbiturates was made along with these studies, using animals of the same kinds living under the same conditions. In rabbits butisol was found to be twice as toxic as phenobarbital sodium. In rats it was approximately three times as active as phenobarbital sodium and also three times as active as ethyl n-butyl barbituric acid (neonal). In white mice it proved to be about half as toxic as pentobarbital sodium, about two-thirds again as toxic as phenobarbital sodium and three times as active as barbital sodium.

In dogs nephrectomy had no apparent effect on the duration of hypnosis due to sec-butyl ethyl barbituric acid.

Its hypnotic action is shorter than that of phenobarbital sodium but longer than that of pentobarbital sodium. Forty per cent of the LD_{50} caused hypnosis lasting approximately seven hours in dogs, two hours in rabbits, and three hours in albino rats.

Like other barbiturates, a large dose injected intravenously in a dog will cause a fall in blood pressure, cutaneous vasodilatation, a decrease in the general tonus of the intact gut and a decrease in the activity of the uterus. On segments of excised rabbit and cat intestine sec-butyl ethyl barbituric acid was less depressant than pentobarbital sodium but more depressant than phenobarbital sodium. This barbiturate was also more depressant on the vagus nerve of the terrapin and on the frog's heart than phenobarbital sodium but less depressant than pentobarbital sodium or ethyl n-butyl barbituric acid (neonal).

The effect of digitalis (gitalin) in hemorrhagic shock in dogs. H. B. HAAG and I. TALIAFERRO. *Dept. of Pharmacology, Medical College of Virginia, Richmond.* Under Dial anesthesia the average fatal dose of gitalin (Verodigen) by intravenous injection was determined on normal dogs and on dogs in which hemorrhagic shock had been produced by the method of Govier (J. Pharmacol. 72: 317, 1941).

For six normal dogs the fatal dose of gitalin was 0.92 mg. per Kg., with an injection time of 87 minutes. For six dogs which had been hemorrhaged 3.6% of their bodyweight, the value was 0.85 mg., with an injection time of 80 minutes. All figures are averages for the respective groups. Since there is no statistically significant difference between the two fatal dose values, it appears that previous hemorrhage does not affect the lethal dose of gitalin in dogs.

A series of experiments was next performed in which all animals were hemorrhaged to shock levels (50–60 mm. Hg maintained for 30 minutes). Half of the animals were then treated with gitalin (15–40% of the average fatal dose intravenously) and the controls received corresponding volumes of saline. Three of these were "paired" experiments; in these the average volume of hemorrhage in the controls was 4.2% of the bodyweight, in the treated 4.6%. Survival time for the controls was 126 minutes; treated, 140 minutes. The injection of gitalin usually provoked a transient rise in blood pressure. The results of all these experiments are in general agreement with Blalock (Arch.

Surg. **15**: 762, 1927) who observed no beneficial effect from digitalis given to dogs after severe hemorrhage, although unlike Blalock's experience, evidence of a particularly harmful influence was not noted.

The relative efficiency of central nervous system stimulants in respiratory depression from morphine. CARROLL A. HANDLEY, DORENCE ENSBERG and H. MORROW SWEENEY. *Univ. of South Dakota Medical School, Vermillion.* A comparison of the effectiveness of amphetamine, caffeine, and metrazol in antagonizing morphine respiratory depression was made on eight human subjects. A fairly consistent degree of respiratory depression was produced by the subcutaneous administration of 0.5 mg. per kg. of morphine sulfate. The maximal action becomes apparent in about one hour and remains constant for several hours thereafter.

As a basis for comparison, respiratory rates were counted and the tidal exchanges and minute volumes measured with the subjects under basal conditions. Morphine was then administered and the above measurements were made at half hour intervals. One hour after the administration of morphine, the stimulant was given and the observations were again repeated.

The results obtained with amphetamine (0.1–0.4 mg./kg., subcut.) was a prompt increase in respiratory rate to near or considerably above the basal level. The tidal exchange and minute volume increased in proportion to the change in respiratory rate. The action of metrazol (3–10 mg./kg., I.M.) was uncertain. There was either no detectable stimulation of respiration or a considerable latent period before mild stimulation became apparent. Caffeine (10–15 mg./kg., subcut., as caffeine sodium benzoate) usually produced some degree of stimulation, but its action was weak in comparison with amphetamine.

The effect of bromide administered during embryonic development on learning tests in rats. BEN KING HARNED, HUGHBERT C. HAMILTON (by invitation) and VERSA V. COLE. *Dept. of Pharmacology, Woman's Medical College of Pennsylvania and Dept. of Psychology, Temple Univ., Philadelphia, Pa.* Sodium bromide was administered to pregnant rats from the 3rd through the 20th day of gestation. The daily doses per kilogram of body weight were: group II, 40 mgm., group III, 80 mgm., group IV, 120 mgm. Group 1-C, the controls were given no bromide. After birth the young rats received no bromide except that obtained from the milk of their mothers. They were weaned at 20 days of age and given their first maze-learning test 37 days later. Determinations of bromide, by the Brodie-Friedman method, on blood and urine gave normal values many days before the first maze-test was made. There were 127 rats in the 4 groups analyzed for learning.

Results of Maze Learning. From 61–85 days each animal was given two trials per day in a five culde-sac U-maze. The criterion of errors shows a positive relationship between the number of errors and the strength of the bromide doses. The criterion of time shows that the group which received the highest dose of bromide was significantly slower than each of the other groups but the other groups did not differ reliably among themselves.

The 3-Table Test. This test consisted of daily runs for 18 days and was started when the rats were approximately 106 days of age. For each criterion; error scores, time scores, and "passing" the control group did much better than the bromide groups.

Influence of sex upon resistance to ouabain in the rat. HARALD G. O. HOLCK and KAZUO K. KIMURA (by invitation). *Dept. of Physiology and Pharmacology, College of Pharmacy, Univ. of Nebraska, Lincoln.* Ouabain, 1 per cent in 0.9 per cent NaCl solution, was injected subcutaneously into 885 albino rats. The LD_{50}'s were alike in the two sexes at the age of 1 month, but at 2 months the females required 23, at 4 months 97 and at 9–11 months 33 per cent more than corresponding males. In contrast to ouabain, average lethal doses of strophantin K were similar in the two sexes in 83 six to ten months old rats. Sex-difference to ouabain was also readily shown by administering 5 to 7 mg. per Kg. (Penick Optimo or Merck) every 5 (but not 10) minutes subcutaneously or intraperitoneally, or 2.5 mg. per Kg. intravenously every 3 minutes to normal or pentobarbitalized rats; but not to rats under urethane anesthesia.

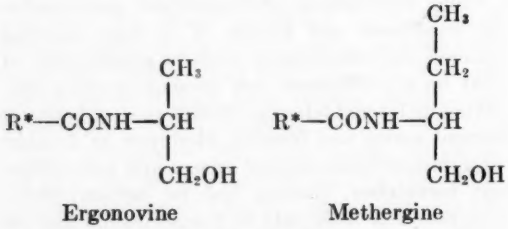
The larger males have relatively smaller hearts than females of similar age; however, results with males and females of the same size or with administration of ouabain per estimated heart instead of body weight still showed significant sex-difference.

Using intravenous administration, pentobarbital anesthesia and groups of 12 rats, spaying lowered the resistance to ouabain significantly so that no sex-difference was present between castrated males and females, though marked between normal males and females. However, in 2 other experiments upon smaller groups and with different techniques, spaying had no certain effect. Castration of male rats in 3 experiments had no significant effect upon tolerance to ouabain, nor did administration of estrogenic hormones to one small group of spayed females alter the resistance. A significant sex-difference existed between unilaterally adrenalectomized rats. [*This work was aided by a grant from the Committee on Therapeutic Research, Council on Pharmacy and Chemistry, American Medical Association and by supplies of ouabain and pentobarbital from S. B. Penick &*

Company and Eli Lilly and Company, respectively.]

d lysergic acid d l hydroxybutylamide 2 - a synthetic oxytocic. II. Preliminary pharmacologic studies. A. C. KIRCHHOF (by invitation), N. M. PHATAK, N. A. DAVID and (by invitation) C. A. RACELY. *Dept. of Pharmacology, Univ. of Oregon Medical School, Portland.* Initial investigation of d lysergic acid d l hydroxybutylamide 2 (Methergine-Sandoz) has indicated that it is markedly oxytocic. Therefore further pharmacologic study has been undertaken. In rats the human therapeutic dose (0.2 mgm.) per 10 grams of rat given subcutaneously had no lethal effect. In doses of 120 mgm. per kilogram administered over a period of 3 days gangrene of the tail did not result. In 6 dogs under light sodium pentobarbital anesthesia, methergine slightly enhanced the adrenalin effect, did not raise the blood pressure and, in doses ranging from 0.2 to 1.2 mgm. had little effect on the respiration. Using the Dreser apparatus in anesthetized rabbits, the respiratory rate and volume was found to be increased. In unanesthetized rabbits the respiratory rate was increased and but slight hyperthermia was noted when methergine was given intravenously in large doses (1.8 mgm. per kilogram).

Studies on d lysergic acid d l hydroxybutylamide 2—a synthetic oxytocic. I. Uterine studies. A. C. KIRCHHOF and W. M. WILSON (introduced by N. A. David). *Dept. of Pharmacology, Univ. of Oregon Medical School, Portland.* The present scarcity of ergot and the small yield of ergonovine from the crude drug has led to the continued investigation of the chemistry and pharmacology of lysergic acid derivatives. Stoll and Hofmann of Basel have synthesized, among several other derivatives, d lysergic acid d l hydroxybutylamide 2 (Methergine-Sandoz). The general formula for this compound, as compared with ergonovine, may be shown as follows:



Ergonovine Methergine

R* represents lysergic acid molecule.

In preliminary investigations methergine was found very utero-active on both rabbit and guinea pig isolated uterine strips in concentrations comparable to ergonovine. Methergine did not reverse the adrenalin response on isolated rabbit uteri as does ergotamine. Relaxation of the isolated guinea pig jejunum was noted indicating slight adrenergic effect. No effect was observed on the isolated virgin dog and rat uteri. In a series of 22 human cases administration intravenously of methergine in doses of 0.2 mgm. in the third stage of labor decreased the blood loss and time from birth of baby to delivery of placenta. Methergine compares favorably with ergonovine in regards to its oxytocic effects.

Comparative effects of pitocin and pitocin tannate in oil on the intact rabbit uterus. A. C. KIRCHHOF and W. M. WILSON (introduced by N. A. David). *Dept. of Pharmacology, Univ. of Oregon Medical School, Portland.* The effects of pitocin and pitocin tannate in oil were studied on 8 rabbits using the Reynolds' technic as modified by Kirchhof and David (West. Journ. Surg., Obs. & Gyn. **51**: 277, July, 1943). The unanesthetized intact rabbit provided with uterine fistula is used and recordings are obtained by photographing the fluctuations in a water manometer connected to a balloon inserted into the uterus. Pitocin tannate in oil given intramuscularly in doses up to 8 units did not on any occasion cause tetany whereas pitocin produced an initial tetanic stimulation followed by rhythmic contractions. In general, 2 units of pitocin produced contractions, after the original tetany, of approximately the same height and frequency as 5 units, intramuscularly, of pitocin tannate. The onset of action of pitocin tannate was delayed from five to ten minutes but the duration of the full effect lasted on the average over two hours. Page (Proc. Soc. Exper. Biol. & Med. **52**: 195, 1943) used pitocin tannate in oil clinically and felt that this preparation had the same inherent disadvantages as other pitocin preparations in the induction of labor. Dieckmann and Kharasch (Am. J. Obstet. and Gynec. **44**: 820, 1942), on the other hand, reported clinical success in labor with the use of another long acting pituitary preparation, solution of posterior pituitary sulfonate. Regardless of the possible clinical use of pitocin tannate in oil, from the experimental standpoint we feel that this preparation may be a useful laboratory tool for the experimental evaluation of uterine antispasmotics. Investigations are now being continued using this drug in this way.

Some circulatory effects of positive pressure respiration during anesthesia. P. K. KNOEFEL, J. P. HOLT (by invitation), C. QUINN (by invitation) and A. M. AMBROSE. *Depts. of Pharmacology and Physiology, Univ. of Louisville School of Medicine, Louisville, Ky.* Positive pressure anesthesia which has been recommended for clinical use with nitrous oxide leads to stagnant anoxia. Seven barbitalized dogs respired for three hours from an oxygen-filled spirometer, weighted to give a pressure 7 mm. Hg above atmospheric pressure. At the end of this period, mean arterial pres-

sure was 12 mm. Hg below, femoral venous pressure 3.7 cm. H_2O above, and cardiac output (determined by the direct Fick principle) 56 per cent of the control values. The reduction in blood flow and increase in venous pressure did not, however, lead to a reduction in plasma volume. In five similar experiments, plasma volume determined with the dye T-1824 was 3 per cent above the control values after the three hour period. Hematocrit determinations indicated an increase of 14 per cent in blood volume, chiefly as the result of an increase in red cell mass.

Simple rapid method for the estimation of sulfonamides. THEODORE KOPPANYI and A. EARL VIVINO. *Dept. of Pharmacology and Materia Medica, Georgetown Univ., School of Medicine.* Hallay applied Runge's aniline test to the qualitative detection of sulfonamides using wood fiber paper (limit of sensitivity 1:10,000). Bogen used the same test for qualitative urine analysis.

White wood fiber paper obtained from a single source was used for the semi-quantitative estimation of sulfonamides in urines, blood filtrates, plasma, serum and other body fluids. The general technique of the test is as follows: Porcelain white color reaction spot plates having uniform hemispherical depressions in the glazed surface were used for comparing the colors developed on uniform circular test papers cut with a punch. Standard solutions of sulfonamides from 0.1–10 mg. per cent in dilute HCl or trichloracetic acid (0.5 cc total volume) were placed in the depressions of the spot plate and circular test paper then added. The orange yellow colors developing on the test paper varied directly in intensity with concentration. This step was necessary to accustom the observer's eye to the gradations of the yellow color of the test papers. Volumes of 0.5 cc of acidulated urines, blood filtrates, plasma, serum or saliva were placed in the depressions and the color on the paper matched against the color of the paper placed in the appropriate standard solutions. Care must be taken that the acidity be approximately the same in the standards and test samples.

Comparing the color of the test paper of the unknown with standards such as 0.3, 0.5, 1.0, 3.0, 5.0, 10 and 20 mg. per cent will immediately determine the approximate range of concentration of the unknown, which then may be more accurately read by comparing with intermediate standards or by standard colorimetric procedures.

The maximum sensitivity of this test is about one part per million and is at least as specific as the diazotization tests for sulfonamides.

The pharmacology and anesthetic properties of ispropenyl vinyl ether (propethylene ether). JOHN C. KRANTZ, JR., C. JELLEFF CARR, AMOS G. HORNEY and WILLIAM E. EVANS, JR. *Dept. of Pharmacology, School of Medicine, University of Maryland.* Isopropenyl vinyl ether (Propethylene Ether) which is isomeric with Cyprethylene Ether or cyclopropyl vinyl ether is a volatile, colorless liquid with a characteristic ethereal odor. It boils at 55°C. and has a specific gravity of 0.786 at 20°C. The compound exhibits anesthetic properties when administered to various species of laboratory animals. Its potency is three to four times that of ethyl ether. In man, Propethylene Ether produces good surgical relaxation and its anesthetic syndrome is marked by the rapidity with which the patient recovers from the anesthesia.

Irreversible damage of the central nervous system by barbiturate in cats. STEPHEN KROP (by invitation) and HARRY GOLD. *Dept. of Pharmacology, Cornell Univ. Medical College, New York, N. Y.* In a recent study of iso-amyl β-bromallyl barbituric acid, a permanent and irreversible damage of the central nervous system was observed in cats. The compound was administered by vein, by mouth, and by rectum to a total of 210 cats in doses varying from 30 to 200 mg. per kg., the lowest dose being in the range of human therapeutic doses. Approximately 50% of the animals died. Of the survivors, about 7% showed motor and postural disturbances suggesting diffuse involvement of the central nervous system which continued for several months, the animals in other respects remaining well. These permanent changes in the central nervous system resulted from doses as low as 30 mg. per kg. They were not related to the depth or duration of the narcosis.

The study was then extended to explore the possibility of this phenomenon in the case of other barbiturates in common use, namely, seconal (similar to the above barbiturate but without bromine), pentobarbital (a rapidly acting barbiturate), pernoston (similar to the first barbiturate except for the iso-butyl taking the place of the iso-amyl group), and phenobarbital, a representative barbiturate of long duration of action. For these experiments, 110 cats were used, approximately equally distributed between the various compounds. These doses varied from 30 to 200 mg. per kg. by oral administration. One-third of the animals died. The survivors recovered completely.

The iso-amyl β-bromallyl barbituric acid was tested in 20 dogs with 30 mg. per kg. by mouth. In these also the recoveries were complete.

These results indicate that some barbiturates are capable of producing permanent damage of the central nervous system in the cat. The dog seems to be resistant.

The metabolic fate of procaine in the dog. EDWARD LARSON. *Dept. of Pharmacology, Temple Univ. School of Medicine, Philadelphia, Pa.* The object of this investigation was to recover procaine or its metabolic products in pure form from urine of animals which had received the drug.

Dunlop (1935), Goldberg et al. (1943) and others have reported the elimination of compounds which give positive chemical tests for procaine and p-aminobenzoic acid. Recently Kisch et al. (1943) have isolated p-aminobenzoic acid from human serum.

In the present study, a total of 10 gm. of procaine hydrochloride was given subcutaneously to two, twelve kilogram dogs over a period of three days and urine was collected daily for ten days. Quantitative analysis indicated that virtually all of the procaine is eliminated as such, as p-aminobenzoic acid, or their equivalent in the form of an unconjugated primary aromatic amine. The urine was extracted in continuous extractors in alkaline and acid mediums with ethyl ether, ethyl acetate, petroleum ether or benzene. Though ethyl ether was the most satisfactory, only small amounts of material could be recovered. Chemical tests on extracts from an acid medium of the urine from the first 5 or 6 days indicated the presence of an amine, presumably p-aminobenzoic acid and of small amounts of procaine in extracts from an alkaline medium. Tests for local anesthetic activity were positive with extracts from an alkaline medium but attempts to crystallize procaine or any of its products were not successful. Extraction of dried urine with volatile solvents gave no further information. No aminohippuric acid or glycuronates could be isolated.

The subcutaneous implantation of sulfamerazine and sulfadiazine in mice. ALBERT R. LATVEN (by invitation) and ARNOLD D. WELCH. *Dept. of Pharmacology, Medical-Research Division, Sharp and Dohme, Inc., Glenolden, Pa.* Chemotherapeutic evaluation of sulfonamides *in vivo* requires the maintenance of essentially constant concentrations of sulfonamide in the blood of infected animals. This has been attained in mice by the subcutaneous implantation of pellets (25 mgm. sulfamerazine or sulfadiazine and 5 mgm. methyl cellulose) which produced a peak sulfonamide concentration in the blood within 24 hours; the concentration fell rapidly, leveled off on about the fifth day, and thereafter decreased very gradually. This "plateau" concentration varied with the number of pellets implanted and was used for the chemotherapeutic evaluation of sulfamerazine and sulfadiazine. Twice as many pellets of sulfadiazine as of sulfamerazine were required to produce similar concentrations in the blood. About seven days after implantation mice were bled from the tail for the determination of the concentration of free sulfonamide and injected intraperitoneally with a suspension of virulent organisms. The mortality was recorded over a period of seven days; the percentage of mice surviving infection was plotted against blood concentration and the SBC_{50} (Survival Blood Concentration 50 per cent) was calculated.

Preliminary results with streptococcal and pneumococcal infections indicate that this technique is well adapted to the evaluation of sulfonamides such as sulfadiazine and sulfamerazine, which are slowly excreted by the kidneys. It has not been possible to maintain effective "plateaued" blood levels with the more rapidly excreted derivatives of sulfanilamide, such as sulfathiazole.

Factors influencing the absorption of mercury from calomel ointments applied to the skin. EDWIN P. LAUG, ELIZABETH AUGHEY and ERNEST J. UMBERGER (introduced by Herbert O. Calvery). *Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington, D. C.* Inunction of rat and rabbit skin with various types of calomel ointments resulted in prompt increase in mercury concentration of liver and kidney, roughly proportional we believe to amounts absorbed. Using a procedure wherein exposure area, inunction time, period of contact, and amount of calomel per kg. body weight were kept constant, the effect of factors influencing the penetration of mercury through the skin were studied. Poor absorption of mercury was noted from lanolin (hydrous or anhydrous), mineral oil and petrolatum; good absorption from lard and corn oil. A paste of propylene glycol and calomel gave outstanding absorption; by contrast, a paste of water and calomel gave poorest absorption. Combinations of some of the above vehicles showed that while lanolin by itself was poor, a 50–50 mixture with lard gave mercury absorption better than from either alone. Dilution of an ointment base with a solid, such as sulfathiazole or talcum, materially reduced absorption of mercury; in fact, "stiffening" by other means appeared to exert a similar effect. The state of subdivision of calomel proved important; significantly more mercury penetrated from micronized than from ordinary powdered calomel. Covering the inuncted area with a more or less air-tight rubberized cloth increased mercury absorption, not only from water soluble but also from grease bases. It would appear that the type of base, whether grease, vanishing cream or cold cream, is not the principal factor in the absorption of mercury.

Vascular permeability and fragility. III. Potentiation of toxic doses of epinephrine by sodium bisulfite as revealed by pulmonary hemorrhage. H. C. LAWSON (by invitation) and C. H. THIENES. *Dept. of Pharmacology, Univ. of Southern California, Los Angeles.* Rats of 100 to 210 grams were injected subcutaneously with varying doses of epinephrine in 1:1000 solution, with and without sodium bisulfite. Injections of epinephrine at one

site and of bisulfite at another site were also made. The LD_{50} dose of epinephrine was reported by Richards (Richards, R. K., J. Pharmacol. and Exper. Therap., **79**: 111, 1943) to be 5.3 mg/K. In our experiments, this dose killed only 1 out of 24 rats. The rats were subsequently killed with pentobarbital sodium and autopsy revealed a moderate degree of lung hemorrhage. Doses of 1.06 and 2.12 mg/K caused neither death nor lung hemorrhage (25 rats). However, 1.06 mg/K of epinephrine dissolved in 1 per cent $NaHSO_3$ killed 6 of 25 rats and produced roughly four times as much pulmonary hemorrhage as 5.3 mg/K of epinephrine given alone. Five rats were injected with 1.06 mg/K epinephrine in 2 per cent $NaHSO_3$ and 5 with 2.12 mg/K epinephrine in 2 per cent $NaHSO_3$. These doses killed all the rats and caused massive pulmonary hemorrhage.

When epinephrine in a dose of 1.06 mg/K was injected at one site and equivalent volumes of 2 per cent and of 5 per cent $NaHSO_3$ were injected at a distant site, the animals all survived and no lung hemorrhage occurred. [*Aided by a grant from Parke, Davis & Co.*]

Isopropyl alcohol: rate of disappearance from the blood stream. ARNOLD J. LEHMAN and HENRY SCHWERMA (by invitation). *Wayne Univ. College of Medicine, Detroit, Michigan.* The concentration of isopropyl alcohol was determined in the blood by distilling off the alcohol under reduced pressure into a solution of potassium dichromate in strong sulphuric acid. The reduced dichromate was estimated iodometrically. Blood isopropyl alcohol was followed in dogs for variable periods after the intravenous administration of 12.5 per cent, 25 per cent, 50 per cent and 75 per cent of the surely fatal intravenous dose, representing 0.64 cc. to 3.84 cc. per kilogram body weight. The rate of disappearance of isopropyl alcohol from the blood was found to be proportional to its concentration in the body. This is in contrast to ethyl alcohol which disappears at a constant rate. This difference can be accounted for by elimination of isopropyl alcohol by several routes as high concentrations of alcohol were found in the urine, saliva and vomitus.

Effect of cinchona alkaloids in pneumococcus infection in mice. W. S. LOEWE and HARRY GOLD. *Dept. of Pharmacology, Cornell University Medical College, New York, N. Y.* Three types of comparisons were carried out testing the influence of cinchona alkaloids (1) on the survival rate of mice infected with Type I pneumococcus, (2) on that of sulfanilamide-treated infected mice, and (3) on that of penicillin-treated infected mice. Each experiment consisted of a group of 3 to 12 controls, and a similar group of mice simultaneously infected with the same dose of pneumococci and treated with cinchona alkaloids. One culture of pneumococci was used. It was distributed into vials and dried at low temperature in vacuo. A virulence test was made in the case of each experiment, and a dose of organisms used which killed some, but not all, the control mice. The dose of pneumococci, the single doses of the cinchona alkaloids, the intervals between then, and the number of prophylactic and curative doses were varied from one experiment to another. The doses of the cinchona alkaloids alone and in combination with sulfanilamide varied from those in the range of therapeutic doses for humans to toxic but sublethal doses for uninfected mice as determined in control experiments. The results thus far are based on experiments with approximately 800 mice.

The results are summarized in the table.

Drug	No. of experiments	Average P.M.D.
Quinine	16	+18.3
Quinidine	5	+15.0
Optochin	2	−33.3
Sulfanilamide	11	−14.5
Penicillin	4	−42.0
Quinine + Sulfanilamide	5	+72.0
Quinidine + Sulfanilamide	4	+8.5
Optochin + Sulfanilamide	2	−15.5
Quinine + Penicillin	4	+58.3
Quinidine + Penicillin	1	+20.0

P.M.D. (−) diminished mortality; (+) increased mortality.

The influence of treatment on infected animals is indicated by a change in the mortality rate and is expressed as the percentage difference (P.M.D. —average of several experiments) between the per cent mortalities of the treated and corresponding control groups.

In the borderline doses used, optochin, sulfanilamide, and penicillin produced relatively small improvement in the mortality rate as was to be expected. It may be noted, however, that quinine and quinidine not only diminished the recovery rate from pneumococcus infection but diminished the recovery rate in the sulfanilamide and penicillin-treated animals.

Pitressin tannate on water exchange of dogs. ESTHER MACULLA (by invitation), CLIFFORD SPINGARN (by invitation) and MICHAEL G. MULINOS. *Dept. of Pharmacology, College of Physicians and Surgeons, Columbia Univ., New York.* The antidiuretic effect of a single intramuscular dose of pitressin tannate in oil (PTO) persists for 24 to 48 hours in contrast to 3 to 6 hours for the aqueous preparation. Eight normal dogs received daily injections of 5 units (1 cc) of PTO. The urine volume decreased 8 to 30 per cent while its specific gravity rose and water intake decreased 8 to 40 per cent. The urine chloride excretion did not change during the injections. There was no alteration in hemoglobin, hematocrit or NPN values or

in plasma specific gravity. On the first day, 5 of the dogs showed no change in urinary output, an increase in the excretion of chloride of 10 to 20 m. eq. There was a decrease in the water intake of 3 of the dogs, probably due to the loss of solute in the urine.

A water load of 25 cc per kilo given by stomach tube was retained maximally. The dogs refused water for 24 to 48 hours after such a test.

When PTO injections were discontinued, the fluid balance returned to normal in 2 to 7 days depending on the number of injections (7 to 21) However, as long as 9 days after discontinuance of PTO a water load given as above was completely retained.

When the dogs have recovered completely from the effects of PTO and are then limited to a water intake like that taken voluntarily during the PTO, they become extremely thirsty, but the blood and urinary findings are analogous to those under PTO.

Influence of diethylstilbestrol upon the effects of small doses of vasopressin. D. F. Marsh (by invitation), R. A. Woodbury and B. E. Abreu. *Dept. of Pharmacology, Univ. of Georgia, School of Medicine, Augusta.* Stilbestrol administrations (3 mg./kg. per day in man and up to 55 mg./kg. per day for 6 days in experimental animals) markedly modify the effects of pitressin in the male and female of man, dog and rabbit. The antidiuretic and pressor actions become more pronounced and prolonged. Small doses of pitressin which do not appreciably influence electrocardiograms in control experiments do have pronounced effects after 24 hours or more of repeated doses of stilbestrol. The P-R interval may be lengthened, partial heart block sometimes occurs, extrasystoles may occur, and the T wave may be changed. The diphasic blood pressure change showing transient reduction in the arterial pressure commonly obtained with large doses of pitressin, is produced by small doses whenever experimental animals have been pretreated with large doses of stilbestrol.

This modification of the activity of pitressin is not present immediately after the administration of stilbestrol even though the stilbestrol was injected intravenously. It is present 24 hours after the first stilbestrol administration though most observations were made after 36 to 100 hours of stilbestrol administrations.

These data are in accord with the histological observations that estrogens increase the renal toxicity of large doses of vasopressin (Byrom, Lancet **1**: 129, 1939). Pre-eclamptic patients also are unusually responsive to vasopressin (W. J. Dieckmann, Toxemias of Pregnancy, pp. 131–133, C. V. Mosby Co.). [*This work was aided by a grant from Burroughs-Wellcome & Co., Inc.*]

Toxicological studies of phthalylsulfathiazole. Paul A. Mattis and Wilbur M. Benson (introduced by A. D. Welch). *Dept. of Pharmacology, Medical-Research Division, Sharp and Dohme, Inc., Glenolden, Pa.* Phthalylsulfathiazole, 2-(N^4-phthalylsulfanilamido)-thiazole, produced no oral toxicity in mice in doses of 10 grams per kgm., and caused a 2 hour concentration of 2.4 mgm. free and 4.1 mgm. total sulfathiazole per 100 cc. of blood. In commercial rations, levels of less than 10 per cent caused no depression in the growth rate of rats over a period of 30 days.

Monkeys given oral doses of 5.0 grams per kgm. per day (6 doses) for 30 days, demonstrated no histopathological changes, but showed anorexia and weight loss; smaller doses produced no toxic manifestations. Peak concentrations of 0.9 mgm. free and 1.4 mgm. total sulfathiazole per 100 cc. of blood were produced. An average of less than 1 per cent of the dose of 5 grams per kgm. was excreted in the urine.

Sodium phthalylsulfathiazole administered intraperitoneally to monkeys, daily for 10 days, in a dose of 0.1 gram per kgm., produced average 1 hour blood concentrations of 3.4 mgm. free and 11.6 mgm. total sulfathiazole per 100 cc., with an average of 60 per cent of the dose excreted within 8 hours. A mild nephrosis was the only manifestation of toxicity. Toxicity increased progressively with dosage (0.1, 0.33, and 1.0 gram per kgm. daily), and was accompanied by pathological changes limited primarily to the kidneys.

The low concentrations in the blood and the low oral toxicity result from the meager absorption of phthalylsulfathiazole from the gastrointestinal tract and its rapid excretion by the kidneys.

An experimental design for the biological assay of epinephrine. Wm. T. McCloskey, Bert J. Vos, Jr. and R. Blackwell Smith, Jr. (by invitation). *Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington, D. C.* The present official (U.S.P.XII) method for the biological assay of epinephrine employs the principle of assay by successive approximation. Methods based upon this principle are wasteful of data in that no use is made of responses which fail to satisfy the criterion of equality, and also in that the design does not permit an easy, exact estimate of the reliability of individual determinations.

A more efficient design, similar to that proposed by Bliss and Marks (Quart. J. Pharm. Pharmacol., **12**: 182, 1939) for insulin, consists of using two dosage levels, differing by 50 per cent, for both the standard and the unknown preparations. Each dose is given four times, the order being determined by assigning the doses at random to a four by four latin square. Factorial analysis of the

responses gives the most probable potency of the unknown preparation, and the standard error of this observed potency is determined by means of the analysis of variance.

Using the experimental design and method of analysis of data outlined above, ten solutions of known potency, ranging in strength from 55 to 140 per cent of the standard, were assayed on dogs meeting the Pharmacopoeial requirements regarding sensitivity. The maximum deviation of potency found from the actual potency was 14.5 per cent, the minimum was 0.5 per cent, and the mean was 4.9 per cent.

Evaluation of the laxative effect of some commonly used laxative substances: with particular reference to dosage. H. A. McGuigan, F. Steigmann and J. A. Dyniewicz. *Dept. of Pharmacology and Therapeutics and Internal Medicine of the Univ. of Illinois College of Medicine and the Cook County Hospital, Dept. of Therapeutics, Chicago.* The laxative effect of phenolphthalein, cascara sagrada, magnesium sulfate, Karaya gum and bran was tested on normal subjects and on patients complaining of constipation. The dose used was that given in the Pharmacopaeia but in the case of phenolphthalein and cascara, larger doses were also tested. The results show that the official doses for phenolphthalein and cascara were too small to produce a laxative effect in over 50% of the cases; only when the dose was doubled and in constipated patients trebled, did the majority of patients have a laxative effect. The laxative effect was also evaluated from patient's impression of the effect; and also, in some instances, by determining the weight and moisture content of the stools. The patient's statement correlated fairly closely with the results obtained by determinations of the weight and moisture of the stools. It appears therefore that the Pharmacopaeial dose of both phenolphthalein and cascara is not sufficiently large to produce a laxative effect.

d-Tubocurarine Cl. and the liberation of the vagus substance in the turtle heart. A. R. McIntyre and Ray E. King (by invitation) .*Univ. of Nebraska Medical College, Omaha.* A physiological solution containing 0.03 per cent KCl and buffered to pH 6.8 was found to be compatible with both turtle and frog hearts. Each continued a normal rhythm for several hours when perfused with this solution. When the hearts were arranged so that the turtle heart was perfused by means of a cannula inserted into the sinus venosus and the perfusate led into the frog heart by means of a Straub cannula, the hearts survived for the greater part of a day. Stimulation of the turtle vagus caused arrest of both hearts both before and after application of d-Tubocurarine to the doner heart. 3.0 mgs. of d-Tubocurarine Cl. (sufficient to curarize a 10 Kg. dog) applied to the turtle heart did not abolish the vagal action and the perfusate caused arrest of the frog heart. Atropine applied to the frog's heart prevented any action of the perfusate obtained from the turtle's heart. These results show that d-Tubocurarine Cl. does not interfere with the liberation of the vagus substances in the turtle heart.

Influence of d-Tubocurarine-Cl. on the liberation of potassium from frog skeletal muscle. A. R. McIntyre and Ray E. King (by invitation). *Univ. of Nebraska Medical College, Omaha.* Pairs of frog-gastrocnemius muscles were placed in beakers with a small amount of De Boer's solution (a modified Ringer solution). After equilibration in the beaker for 28 minutes, one muscle was stimulated indirectly for 7 minutes with a tetanic stimulus. The other muscle was allowed to remain in the solution, as a control, without stimulation for an equivalent length of time. The same procedure was carried out with another pair of muscles of equal weight, but to each beaker containing the muscle and solution was added one part per thousand of crystalline d-Tubocurarine Cl. The muscles were removed at the end of 35 minutes and the potassium content of the solutions determined. All the muscles lost potassium. The muscles in the beakers to which curare has been added lost more potassium than their corresponding non-curarized pairs. The muscle exposed to curare and indirectly stimulated lost approximately twice as much potassium as the muscle indirectly stimulated and not exposed to curare. It is concluded that curare augments the rate of loss of potassium from muscle *in vitro* under the conditions of the experiment both in indirectly stimulated and non-stimulated muscles.

The comparative toxicity of the veratrum alkaloids. Rafael Mendez (introduced by Otto Krayer). *Dept. of Pharmacology, Harvard Medical School, Boston.* Although pure veratrum alkaloids were repeatedly compared in the past as to their activity in intact, unanesthetized mammals (1), none of the investigators had available pure substances in sufficient number and quantity for the method of comparison chosen to present satisfactory information as to the relative potency of a larger series of these alkaloids under identical experimental conditions.

We examined the following pure substances: Protoveratrine, protoverine, germine, jervine, and rubijervine, from *Veratrum album*, Linn.; and veratridine and cevine, from *Veratrum Sabadilla*, Retz.

To utilize fully the limited quantities of the alkaloids available, white mice of both sexes, weighing from 15 to 30 grams, were used, and each dose was injected to a group of six animals by way of the tail vein. Injections were always made in a period of exactly ten seconds, and the strength of

the solutions was adjusted so as to contain the dose in a volume of 0.1 to 0.4 cc. Protoveratrine, veratridine, cevine, germine, and protoverine were dissolved in molecularly equivalent amounts of hydrochloric acid, buffered to approximately pH 7.0 with sodium bicarbonate, and injected in 0.9% sodium chloride. Jervine and rubijervine were dissolved in a small amount of glacial acetic acid, buffered to approximately pH 6 with sodium bicarbonate, and injected as the alkamine acetate. From the observed mortality for each dose, the deduced mortality was determined according to the method of Behrens (2). The normal equivalent deviation was determined for the percentage mortality as recommended by Gaddum (3), and the average lethal dose, or L.D. 50, was read from the straight line obtained by plotting the logarithm of the dose against the normal equivalent deviation (see table 1).

TABLE 1

The toxicity of the veratrum alkaloids (mice, intravenous injection)

Substance	Empirical formula	Mol. weight	L.D.50 (mgm./kgm.)	L.D. 50 (millimols/kgm.)
Protoveratrine	$C_{39}H_{61}O_{12}N$	751	0.048	0.000064
Veratridine	$C_{35}H_{51}O_{11}N$	673	0.42	0.000628
Jervine	$C_{27}H_{39}O_3N$	425	9.3	0.0219
Rubijervine	$C_{27}H_{41}O_2N$	413	70.0	0.170
Cevine	$C_{27}H_{43}O_3N$	509	87.0	0.170
Germine	$C_{27}H_{43}O_3N$	509	139.0	0.274
Protoverine	$C_{27}H_{43}O_9N$	525	194.0	0.367

Protoveratrine, a tri-acyl-ester of protoverine, is ten times as toxic as veratridine, a mono-acyl-ester of cevine. The alkamines, which are all C_{27} compounds, are much less toxic than the ester alkaloids. The toxic doses (L.D. 50) of jervine, rubijervine, cevine, germine, and protoverine are in the rates of ¼, 2, 2, 3, and 4. There are conspicuous qualitative, as well as quantitative, differences, not only between the ester alkaloids and the alkamines as groups, and between the two ester alkaloids, but also among the alkamines. [*This work was done under the auspices of the Univ. Committee on Pharmacotherapy.*] [*Dr. W. A. Jacobs generously supplied all the alkaloids except veratridine, which was prepared by R. P. Linstead and D. Todd.*]

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Antagonism of the antibacterial action of atabrine and propamidine in vitro by spermine and spermidine. A. KATHRINE MILLER, LAWRENCE PETERS and D. K. BOSSHARDT (introduced by A. D. Welch). *From the Depts. of Pharmacology and Biochemistry, Medical-Research Division, Sharp and Dohme, Inc. Glenolden, Pa.* Silverman and Evans (J. Biol. Chem. **150:** 265, 1943) have described antagonism of the antibacterial action of atabrine with spermine or spermidine. We have found that, although M/2000 atabrine in bactopeptone medium completely inhibited the growth of *Escherichia coli* during an incubation of 96 hours, the addition of M/2000 or M/4000 spermine or spermidine (isolated from pancreas) to M/2000 atabrine caused visible growth in 5 to 6 hours; control tubes showed a similar turbidity in 4 hours. Measuring turbidities photoelectrically at the time when maximal growth in the control tubes was just attained, and using a level of atabrine (M/4000) that barely allowed growth, complete reversal of atabrine inhibition was not produced by the compounds. Antagonism of 1 mol of atabrine was incomplete with approximately 0.4 mol of spermine; with spermidine, 1 mol; with larger amounts antagonism was not increased and with putrescine antagonism was absent. In this medium M/2000 spermine slightly inhibited growth, an effect not noted with spermidine or with M/10,000 spermine.

In salt-glucose-asparagine medium, allowing for the stimulation of growth caused by both spermine and spermidine, partial antagonism was produced by approximately 5 mols of spermine or of spermidine to 1 mol of atabrine. In both media spermine and spermidine slightly antagonized propamidine inhibition but had no effect on the inhibition of quinine, sulfanilamide or sulfathiazole. Mapharsen apparently reacted chemically with spermine since a brown color developed on incubation of mixtures.

Potency of sodium dehydrocholate (decholin sodium) as a diuretic agent in man. WALTER MODELL (by invitation) and HARRY GOLD. *Dept. of Pharmacology, Cornell Univ. Medical College, New York, N. Y.* This was investigated in a group of 25 ambulant patients with advanced heart failure, who were only partly relieved by digitalis and who showed marked additional improvement with potent diuretics. The effect of decholin sodium in a dose of 2 grams in a 20 per cent solution was compared with that of mercupurin intravenously. A dose of mercupurin was alternated at weekly intervals with a dose of decholin or a mixture of decholin and mercupurin. There were in all about 200 injections. The effect was measured by the loss of body weight in the 15 hours following the dose.

The results fall into 3 groups:

(1) Sensitive patients losing an average of 4.6

lbs. after 1 cc. mercupurin. In these the effect of decholin was 40 per cent (14 to 66) as great.

(2) Resistant patients showing no greater weight loss (4.3 lbs.) after twice the dose of mercupurin (2 cc.). These were also more resistant to decholin, the effect of the same dose being only 21 per cent (3 to 33) as great.

(3) The mixture of the two drugs produced a diuretic effect which was substantially a summation of the effects of each.

In one patient the decholin produced an immediate reaction; flushing, giddiness, and vomiting. All experienced the bitter taste.

From determinations of the blood NPN and urinalyses at intervals of two weeks during the course of the study, there was no indication that the mercupurin or the decholin produced any renal damage.

The effect of sulfonamides on the central nervous system in dogs. CHARLES F. MORGAN, SAMUEL A. CORSON, A. EARL VIVINO and THEODORE KOPPANYI. *Dept. of Pharmacology and Materia Medica, Georgetown Univ., School of Medicine.* Sulfathiazole (3–7.5 grams/kg.), sulfapyridine (1.5–4 grams/kg.), and sulfanilamide (3 grams/kg.) were administered orally to 20 dogs in mucilage of acacia suspensions.

Sulfathiazole (9 dogs) produced no visible toxic symptoms beyond salivation, nausea, vomiting and some lassitude.

Sulfapyridine (3 dogs) produced salivation, nausea, vomiting, slight or no ataxia, marked mydriasis and abolition of pupillary light reflex, and after 2–3 hrs. marked clonic convulsions recurring at 12 minute intervals for small doses—higher frequencies for larger doses. Between attacks those receiving the minimal dose recovered fully, showed normal placement and body righting reflexes, (apparently) normal vision and hearing, and occasionally a brief, tetanic convulsion. Recovery took place in about 8 hrs.

Sulfanilamide (8 dogs) produced "gastro-intestinal" toxic symptoms, ataxia, spastic gait, loss of placement reactions, hypalgesia or analgesia, and, after 3–4 hrs., a behavior indistinguishable from the classical decerebrate rigidity (already intimated by Hawking, and Marshall) and apparent absence of vision and hearing, but intact pupillary reflexes. Following the 2½–3 hr. period of rigidity, the animals sometimes collapsed (most righting reflexes absent e.g. deviation but no nystagmus, no landing reflex). Animals recovered in 7–8 hrs. Nembutal 3–10 mg./kg.) abolished the rigidity, metrazol (10 mg./kg.) restored it. One animal received sulfanilamide for 6 consecutive weeks (3 grams/kg. weekly); the onset of the nervous symptoms and the recovery were progressively delayed to about 16 hrs. and 2–3 days respectively.

In resumé, doses, above therapeutic levels, of sulfathiazole produced no apparent neurotoxic symptoms; of sulfapyridine—interference with the pupillary light reflex, clonic convulsions but no rigidity; of sulfanilamide—ataxia, abolition of the placement reactions, rigidity but no convulsions, and no interference with the light reflex.

Choleretic action of certain halogenated fatty acids. JAMES L. MORRISON (introduced by E. L. Jackson). *Dept. of Pharmacology, Emory Univ. School of Medicine, Emory Univ., Ga.* The choleretic action of α-chloropropionic acid, β-chloropropionic acid, α-bromopropionic acid, β-bromopropionic acid and α-bromobutyric, injected intravenously as the sodium salts in dogs lightly anesthetized with sodium pentobarbital, was studied, following the method previously described (Fed. Proc. 2:78, 1943). In each case, with the exception of β-chloroprionic acid, a dose equivalent to 0.25 mM/Kg. resulted in a 200 to 300 per cent increase in bile flow within 30 minutes. In the case of β-chloropropionic this same dose (0.25 mM/Kg.) produced no significant increase in bile flow within four hours, and even trebling the dose (0.75 mM/Kg.) was without effect. The sodium salts of propionic and lactic acids had no significant choleretic action. In the concentrations used none of the compounds affected significantly either the circulation or the respiration. The choleresis observed was similar to that produced by "Decholin," but was of much greater duration.

Effect of inanition on castration cell formation. LEO G. PARMER (by invitation) and MICHAEL G. MULINOS. *Dept. of Pharmacology, College of Physicians and Surgeons, Columbia Univ., New York.* Prolonged inanition results in a depression of the activity of the anterior pituitary gland. This results in atrophy of those endocrine glands which depend for their activity upon the pituitary. The condition so produced has been termed "pseudohypophysectomy" because it and hypophysectomy result in similar hormone gland atrophy.

Castration cells did not appear in the hypophyses of rats which were severely underfed for several months.

Rats were castrated and allowed to feed normally until castration cells appeared as shown by a sample autopsy. These rats were then continuously underfed and autopsied at intervals of from 6 to 265 days. Castration cells were present in the hypophysis of every animal, as in the fully fed castrated controls. Rats which had been castrated 70 days previously were starved completely for 10 days until moribund. The hypophyses contained castration cells.

Rats were castrated and underfed for 74 days. Castration cells appeared in the hypophyses.

Inanition depresses the anterior pituitary severely and the ovaries and adnexa shrink in size to a condition approaching hypophysectomy.

However, enough estrogen is produced to prevent the appearance of castration cells. Since during inanition there is nō increase in the gonadotropic content of the hypophyses of castrate rats (Proc. Soc. Exper. Biol. and Med. **41**: 101, 1939) it is surmised that castration cells do not invariably indicate an increase in the gonadotropic activity of the pituitary.

The relationship of the carotid and aortic mechanisms to digitalis emesis. N. W. PINSCHMIDT. *Dept. of Pharmacology, Medical College of Virginia, Richmond.* The mechanism of digitalis vomiting is still a moot one. Hatcher has advanced evidence indicating that digitalis emesis results from afferent impulses arising in the heart. Dresbach and Waddell, as well as Haney and Lindgren, were unable to confirm this. Haney and Lindgren concluded that the mechanism may be either a direct stimulating effect on the vomiting center or on other structures from which impulses pass via nerves other than those eliminated by them. Because of the importance of the carotid and aortic mechanisms in influencing reflexly certain medullary centers, their possible role in digitalis vomiting was studied in the following experiments.

The effect of an emetic dose of digitoxin (0.15 mg. per Kg.) was observed on seven dogs which had both carotid bodies and sinuses removed by extirpation of segments of the carotid artery from a point just caudal to the origin of the superior thyroid artery to a point slightly cephalic to the origin of the lingual artery. After allowing time for recovery from operation, the digitoxin was administered by intravenous injection. In every case vomiting was as prompt and typical after operation as before.

Six of these dogs survived sectioning of one vagus trunk (in the neck region) and two survived sectioning of both vagi without change in their vomiting response to digitoxin.

It is concluded that vomiting initiated by digitoxin is not abolished by removal of the carotid bodies and sinuses and by denervation of the aortic mechanisms.

An experimental study on pulmonary edema in the rat. FRANZ REICHSMAN (introduced by Arthur Grollman). *Dept. of Internal Medicine, Bowman Gray School of Medicine, Wake Forest College, Winston-Salem, N. C.* It has been claimed (Arch. ges. Physiol. **68**: 231, 1932; J. Exp. Med. **117**: 70, 1939) that marked pulmonary edema may be produced in the rat with regularity by bilateral cervical vagotomy. In 25 piebald rats (strain Mus norvegicus) we obtained pulmonary edema in only approximately two-thirds of our bilaterally vagotomized animals. Approximately one-third showed either no pulmonary edema or pulmonary edema of such minimal degree, that it evidently could not account for the death of the animal. The survival time of many rats after bilateral cervical vagotomy was much longer than was anticipated from the above-mentioned reports. Over one-third of our rats lived longer than 24 hours (up to 88 hours). Although these rats showed, in general, less pulmonary edema than those with shorter survival time, there was often no parallelism between the length of survival and the degree of pulmonary edema the rats developed. To determine whether accidental cutting of the cervical sympathetics was responsible for the failure of some rats to show pulmonary edema, the sympathetics—in addition to the vagi—were cut purposely in 8 rats. The occurrence of pulmonary edema and the survival time in this group were approximately the same as in a group where the vagi only had been cut. The effect of respiratory obstruction in vagotomized rats on the appearance of pulmonary edema is being further studied. [*Aided by a grant from the Dazian Foundation.*]

Dinitrophenol cataract: Production in an experimental animal. BENJAMIN H. ROBBINS. *Dept. of Pharmacology, Vanderbilt Univ. School of Medicine, Nashville, Tenn.* Horner (Arch. Ophthal. **27**: 1097, 1942), stated that all attempts at the production of cataracts with dinitrophenol-sodium (DNP-Na) in experimental animals had failed.

During our studies on the effect of chemicals upon the fowl-pox infection in chicks it was observed that, in chicks receiving DNP-Na in their feed, opacities of the lenses developed soon after they were placed upon the diet.

We have followed this observation with experiments to determine: (1) the concentration of DNP-Na in the diet necessary for the production of cataracts; (2) the age of the chick during which the lenses were susceptible to the drug; (3) the site of lesions in the lens; (4) the duration of the pathological changes while the chick was still ingesting the drug.

DNP-Na was mixed with the feed (Purina Startena) in concentrations from 0.05–0.25%; chicks were started on the mixtures when 10–100 days old; chicks were sacrificed after they had been on the diet from 5 hours to 50 days; chicks have been kept on the diet for 90 days.

Chicks, 10–100 days old, routinely develop cataracts after ingesting diets containing 0.1-0.25% DNP-Na; opacities may develop within 5 hours and persist for 100 days while the drug is ingested; fine vacuoles appear first in the anterior lens fibers—later marked lesions develop in the posterior portion of the lenses and these persist as long as the drug has been given.

Cataracts have been produced by DNP-Na in an experimental animal.

Effect of alcohol and barbiturates on urine output of white rats exposed to low barometric pressures.

HERBERT SILVETTE. *Dept. of Pharmacology, Univ. of Virginia, Charlottesville.* White rats exposed daily to altitude equivalents of 15,000 or 25,000 ft. in low-pressure chambers developed a marked polyuria during the time of exposure. When animals were given access to 5% or 10% alcohol as their sole source of drinking fluid and then exposed to 15,000 or 25,000 ft. altitude equivalent, they also showed a polyuria, which was not, however, as marked as that resulting when water the drinking fluid. This difference appeared to be due to the fact that the fluid intake of the alcohol-fed animals was less than that of the controls. On that basis it may be concluded that the high-altitude polyuria developing in the alcohol-fed animals was relatively as great as the "water" polyuria. Alcohol given in this manner was not diuretic, nor did it otherwise affect the reaction or survival of the animals under low barometric pressures.

Anesthetic doses of pentobarbital-sodium reduced the urine output of rats at 0 ft. This pentobarbital oliguria was still evident when similarly treated animals were exposed to an equivalent altitude of 15,000 ft.; in other words, the high-altitude polyuria did not overcome the barbiturate oliguria. Incidentally, it was observed that rats were more sensitive to barbiturates at high altitudes, and the duration of effect was greater, than at 0 ft. A dose of evipal or pentobarbital which was merely hypnotic at 0 ft. proved to be anesthetic at 15,000 ft.; and an anesthetic dose at 0 ft. was lethal at 15,000 ft. [*This investigation has been made with the assistance of a grant from the Ella Sachs Plotz Foundation.*]

The prolonged administration of quinacrine (Atabrine) and sulfathiazole to dogs. R. BLACKWELL SMITH, JR., LLEWELLYN WELSH and ARTFUR A. NELSON (introduced by Herbert O. Calvery). *Division of Pharmacology, and Chemical Section of Drug Division, Food and Drug Administration, Federal Security Agency, Washington, D. C.* Using 45 dogs, an experiment has been designed to evaluate effects of chronic administration of 2 and 5 mg./kg./day of quinacrine (Atabrine), 50 and 100 mg./kg./day of sulfathiazole, and combinations of the drugs at these levels.

After one year on experiment there have been no clinical signs of quinacrine toxicity, aside from a slight, questionable tendency toward decreased growth. The only sign of toxicity in the sulfathiazole dogs is a conjunctivitis. No data have been obtained to indicate that simultaneous administration of the two drugs is contraindicated Bromsulfalein tests on dogs receiving the high level of quinacrine, and also the high level of both drugs concurrently, are negative. Hematological studies have yielded no positive findings to date. Gross and histopathological examinations of two dogs (not from the group of 45 mentioned above) sacrificed after receiving the high level of quinacrine for 11 months disclosed no lesions attributable to the drug.

The quinacrine level in the blood of dogs chronically receiving 5 mg./kg./day varies within the average limits of 0.075 and 0.25 mg./L., and the peak concentration is usually reached within 2 hours after administration. Administration of sulfathiazole does not appreciably affect these levels. When quinacrine is withdrawn after 4 to 5 months of medication, blood samples exhibit a greater than normal fluorescence for approximately 28 days and urine samples for at least 40 days.

Pitressin tannate on desoxycorticosterone acetate hyposthenuria. CLIFFORD SPINGARN (by invitation), ESTHER MACULLA (by invitation) and MICHAEL G. MULINOS. *Dept. of Pharmacology, College of Physicians and Surgeons, Columbia Univ., New York.* In normal dogs injections of pitressin tannate in oil (PTO) 5 units daily reduced the water exchange and raised the urine specific gravity. In 4 dogs made hyposthenuric by injections of desoxycorticosterone acetate (DCA), 10 mg. daily, PTO in daily doses of 5 to 20 units reduced the voluntary intake of water from 1936 cc to 1147 cc. The urine volume fell from 1870 cc to 1084 cc and its specific gravity rose from 1.005 to 1.010. The fluid exchange was reduced about 40 per cent by PTO independently of its magnitude.

A water load of 25 cc per kilo given by stomach tube to DCA dogs is excreted promptly while PTO does not completely inhibit its passage out of the kidney as it does normally.

DCA increased the average daily excretion of chloride in 2 dogs and this effect was reversed by PTO. In 2 dogs DCA did not change the chloride output and PTO had no effect.

During DCA hyposthenuria water intake limited to that during PTO reduced the urine volume and raised its specific gravity similarly to that from PTO. Progressive reduction of the high water intake to the normal levels of 100 to 400 cc for 3 to 7 days resulted in loss in weight, excessive thirst and dehydration. The specific gravity of the urine rose from 1.005 to 1.027.

Effect of administration of large doses of vitamin A on the plasma vitamin A level of patients with renal disease. F. STEIGMANN and HANS POPPER. *Dept. of Therapeutics of the Cook County Hospital and the Hektoen Institute for Medical Research, Chicago, Ill.* The response of the plasma vitamin A level following the intake of 75,000 units of vitamin A was examined in 23 instances on 17 patients with renal disease and compared with that of hospital controls. The fasting plasma vitamin A level was found elevated in renal disease. The response to the test dose was in the majority of cases much more marked than in the controls. Whereas in the

hospital controls the elevation of the plasma vitamin A level returned almost to normal at the end of twenty-four hours, it persisted beyond this time limit in the renal cases.

Effect of vitamine B_1 and cocarboxylase on the synthesis of acetylcholine in vitro. CLARA TORDA and HAROLD G. WOLFF. *New York Hospital and the Depts. of Medicine (Neurology) and Psychiatry, Cornell Univ. Medical College, New York, N. Y.* Thiamine chloride (vitamine B_1) and thiamine pyrophosphate (cocarboxylase) inhibit choline esterase (Glick and Antropol). The concentrations required for such inhibition are higher than those found in the serum, but probably do not exceed the concentrations present in some tissues. Remarkably enough, thiamine chloride, even in higher concentrations, does not help patients benefited by other inhibitors of the choline esterase (myasthenia gravis). The above observations suggested the investigation of the effects of the thiamine compounds on the synthesis of acetylcholine.

The synthesis of acetylcholine was studied following the method of Quastel, Tennenbaum and Wheatley. Uniform samples of homogenized frog brains were used as a source of the enzyme, while human serum or human spinal fluid and the frog brain itself supplied the substrate. The amounts of free and total acetylcholine synthesized was assayed biologically with the sensitized rectus abdominis muscle of the frog.

Both thiamine chloride and thiamine pyrophosphate, in biological concentrations (3.10^{-6}M), slightly increased the synthesis of acetylcholine (15 per cent average). Both thiamine chloride and thiamine pyrophosphate, in concentrations depressing the activity of choline esterase, also depressed the synthesis of acetylcholine. Thiamine chloride was a more potent depressor than was thiamine pyrophosphate.

Since concentrations of vitamine B_1 and cocarboxylase inhibiting choline esterase also inhibit the synthesis of acetylcholine *in vitro*, no significant aid can be expected from these substances for patients with disorders resulting from decreased synthesis of acetylcholine.

REFERENCES: GLICK, D. AND ANTROPOL, W. Proc. Soc. Exp. Biol. & Med. **42**: 396, 1939. QUASTEL, TENNENBAUM AND WHEATLEY. Bioch. J. **30**: 1668, 1937.

Effect of vitamine K on the activity of choline esterase and on the contraction of striated muscle. CLARA TORDA and HAROLD G. WOLFF. *New York Hospital and the Depts. of Medicine (Neurology) and Psychiatry, Cornell Univ. Medical College, New York, N. Y.* Since, under physiological conditions, vitamine K has the ability to react with enzymes containing the —SH group (Summerson), the effect of vitamine K on the activity of choline esterase was investigated in the following.

The activity of choline esterase was studied following the method of Ammon using the Warburg apparatus. No significant decrease of the activity of choline esterase in the presence of vitamine K was found. Similar conclusions were drawn from the observation that vitamine K did not increase the sensitivity of the rectus abdominis muscle of frog to acetylcholine.

On the other hand, vitamine K in low and higher concentrations (1.10^{-7}–1.10^{-3}M) significantly increased the response of the striated muscle to direct chemical stimuli such as potassium (25 to 450 per cent respectively above the control). This increase in muscle contraction is probably due to changes in the metabolism of the muscle because of the presence of the vitamine.

REFERENCES: SUMMERSON, W. H. Federation Proc. **2**: 72, 1943. AMMON, R. Pflüger's Archiv **233**: 486, 1933.

Irritation studies on ointments. BERT J. VOS, JR., JOHN H. DRAIZE, GEOFFREY WOODARD (by invitation) and VIRGINIA D. JOHNSON (by invitation). *Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington, D. C.* Irritancy of 230 ointments and of their various components was studied by means of: (1) patch tests on intact and abraded skin of albino rabbits; (2) administration into conjunctival sac of rabbits; (3) application to mucous membrane of rabbit's penis; and (4) patch tests on man. Observations were made at 24 hours and in many instances also at 1 and 72 hours. Irritation was graded on an arbitrary scale.

With 20 ointments, each containing a different organic arsenical at a 0.024M concentration in a vehicle consisting of 75 parts propylene glycol, 17 parts glycerol monostearate and 8 parts cetyl alcohol, there was no significant correlation between the results of the patch tests on man and any of the animal tests. In contrast, 12 ointments containing 15 per cent sulfathiazole and 30 per cent calomel in various types of bases showed significant correlation between human patch test scores and those of the rabbit eye tests ($r = +0.78$), the patch tests on the intact ($r = +0.58$) and the abraded ($r = +0.71$) rabbit skin, but not those of the rabbit penis ($r = +0.04$).

The majority of arsenical ointments were moderately irritating to rabbit skin, particularly when abraded. Sulfathiazole and calomel ointments were only mildly irritating.

Surface active agents were present in 63 ointments. Concentrations above 0.5 per cent consistently increased the irritation of the ointment. The rabbit's skin and more especially its cornea was more sensitive to irritation by these agents than human skin.

A respiratory reflex originating from the thoracic wall of the dog. R. W. WHITEHEAD and W. B. DRAPER. *Dept. of Physiology and Pharmacology, Univ. of Colorado, Denver.* Respiratory arrest was produced and maintained for considerable periods by the intravenous injection of 2.5% pentothal sodium using a mechanical injector. Oxygenation was maintained during respiratory arrest by placing a mouth hook flowing 12 liters of oxygen a minute in the dog's mouth or by attaching a sensitive spirometer filled with oxygen and provided with a soda lime absorber to a tracheal cannula. (See accompanying abstract on diffusion respiration.)

The reflex is elicited by the application of light, non-deforming pressure to a localized area of the chest wall about 2 inches in diameter, in the region of the 4th rib and interspace about 1½ inches from the midsternum. The reflex has the following characteristics: The adequate stimulus is light pressure. The induced respiratory act is largely diaphragmatic and always moves a substantial volume of gas. The reflex is inhibited by anoxia, shock and very deep levels of anesthetic depression. With lightening anesthesia, it reappears on an average of 4 minutes before the resumption of spontaneous breathing. It is a more efficient stimulus to respiration than is either tongue traction or anal stretching. The reflex has also been demonstrated in the dog in respiratory arrest produced by chloroform and in the dog, rabbit and rat depressed by pentobarbital sodium.

The reflex is obtained following very light pressure applied to the lower end of the scalenus medius muscle and tendon, and to the upper end of the rectus abdominis muscle and tendon. Trauma to these structures causes it to disappear.

Skin penetration and localization of sulfathiazole in rabbits from various ointment bases. GEOFFREY WOODARD, CLARENCE D. WRIGHT, O. L. EVENSON, RUTH R. OFNER, DIANA S. KRAMER, PAUL M. JENNER and VIRGINIA D. JOHNSON (introduced by Herbert O. Calvery). *Division of Pharmacology, Chemical Section, Drug Division and Cosmetic Division, Food and Drug Administration, Federal Security Agency, Washington, D. C.* Sulfathiazole levels determined by the Bratton-Marshall method in blood samples taken 2 and 5 hours and in catheterized urine samples 3½, 6½ and 24 hours after applying the ointment to 150 cm.² of the dorsal clipped intact skin were used as a measure of penetration.

Skin localization was determined by analysis of definite areas of skin taken after thorough removal of the ointment with soap and water.

Ointments were tested comparatively using suitably designed experiments and sufficient animals so that differences reported here are statistically signficant.

The following observations were made: (1) Sulfathiazole was absorbed poorly from fat or oil bases, slightly from water-in-oil emulsions and aqueous jelly, moderately from oil-in-water emulsions, and best from bases with high glycol content, propylene glycol being superior. (2) A sodium sulfathiazole or a micro-crystal sulfathiazole oil-in-water emulsion ointment failed to give absorption comparable to the glycol bases. (3) The addition of certain surface-active agents, notably sodium lauryl sulfate or an aryl alkyl poly-ether alcohol improved penetration while certain others did not. These substances increased irritation. (4) Skin penetration or localization from 5% equaled that from 20% sulfathiazole ointments. (5) Inclusion of calomel or organic arsenicals did not effect skin penetration. (6) Skin localization was greatest with glycol bases and increased with time of contact of ointments. (7) Covering the site of application increased penetration.

Influence of neostigmine on arterial pressure and uterine activity of eclamptic patients. R. A. WOODBURY, B. E. ABREU, R. TORPIN (by invitation) and P. H. FRIED (by invitation). *Depts. of Pharmacology and Obstetrics and Gynecology, Univ. of Georgia School of Medicine, Augusta.* In 3 gravid eclamptic patients neostigmine reduced the arterial pressure from 185/105 to 143/83, from 220/125 to 124/92, and from 145/82 to 100/60. In 2 gravid eclamptic patients neostigmine failed to reduce the arterial pressure. In fact it raised the arterial pressure 20 mm. Hg is one of these patients. This elevation could result from nicotinic action of acetylcholine. Neostigmine did not change or elevated slightly the arterial pressure in four control patients: two were hypertensive patients, one of whom was pregnant. One was a normal control gravid patient and one was a 10 hours post partum eclamptic patient in whom neostigmine had been effective 20 hours earlier.

In the gravid patients (8 to 9 months) neostigmine appeared to induce labor. The uterine activity was normal and delivery was uncomplicated in 5 of the 7 patients. In the other two (multiparous eclamptic patients) the uterus became hyperreactive and labor was dangerously prolonged (36 and 48 hours).

Individual susceptibility appeared to vary greatly. The drug was administered as follows: One to three intramuscular injections of 0.25 mgm. mgm. at intervals of 90 minutes followed at hourly intervals by one or two hourly intravenous injections of 0.02 to 0.25 mgm. The uterine and vascular effects of neostigmine appeared rather suddenly but only after an elapse of one or two hours after the last injection. Chill and slight temperature elevation accompanied the rather sudden appearance (10 minutes) of the fall in arterial pressure. In the pregnant patients the

drug was discontinued when the manifestations of nicotinic effects first appeared. While this study offers a possible mode of treatment, it and cholinesterase studies in placentas from normal and preeclamptic patients (see Abreu and Woodbury, these abstracts) stress the importance of acetylcholine activity in eclampsia. Abnormal responses to vasopressin may also contribute to the pathological changes in eclampsia (see Marsh, Woodbury, Abreu, these abstracts). [*This work was aided by a grant from Eli Lilly and Company.*]

The effect of atabrine on the oxygen consumption of rat tissues. C. I. WRIGHT and JEAN C. SABINE. *Division of Physiology, National Inst. of Health, Bethesda, Md.* Atabrine (above 0.0002M) inhibits the O_2 consumption of rat liver, kidney and brain. The O_2 consumption of liver slices from a fed rat first increases (± 50 per cent) and then falls to approximately 5% of normal. No rise in O_2 consumption occurs if the rat is fasted 24 to 48 hours. Tissues thoroughly poisoned with atabrine are unable to oxidize lactate, pyruvate, citrate, malate or fumarate, but can oxidize succinate, consuming O_2 roughly equivalent to a conversion to fumarate. Atabrinized tissues also oxidize p-phenylene-diamine, indicating that the cytochrome oxidase system is intact.

Atabrine inhibits Kreb's kidney preparation of d-amino-acid oxidase, using dl-alanine as substrate. The prosthetic group of the d-amino-acid oxidase, prepared by heat or methanol treatment of the kidney extract, partially protects the d-amino-acid oxidase against atabrine. The same preparation, when added with atabrine to tissue slices, prevents the fall in O_2 consumption. The indications are, therefore, that atabrine interferes with the yellow enzyme systems.

Tissue distribution and retention of mapharsen following intravenous administration. HAROLD N. WRIGHT. *Univ. of Minnesota Medical School.* Maximum tolerated doses of mapharsen (15 mgm./Kgm.) were administered to rats and the distribution and retention of the drug was determined in eleven organs or tissues at a series of time intervals ranging from 15 minutes to 28 days after administration.

The majority of the drug leaves the blood stream rapidly, the mean fraction remaining ¼, ½, and 1 hour after administration being 17.11, 26.00 and 14.80 per cent. The tissues or organs which had taken up the largest amount of drug were muscle, small intestine (thoroughly freed of all contents) and kidneys, which collectively accounted for 37.46, 40.27 and 42.31 per cent of the administered dose at these same time intervals. Other tissues or organs retaining appreciable amounts of the drug were liver, skin and bone which together contained 13.51, 10.29 and 11.10 per cent at corresponding time intervals.

The blood concentration falls to minimal values of 6.60 and 6.59 per cent at 6 and 12 hours, with a secondary rise to 14.64 per cent at 24 hours, similar to that seen with the arsphenamines (Rodman and Wright, Jour. Pharmacol. and Exper. Therap., 79: 140, 1943 and others). Mapharsen differs from the arsphenamines in that the blood concentration remains high for a long period of time, being 15.59, 20.36 and 20.60 per cent at 48, 72 and 96 hours respectively, and indeed this accounts for the greater part of the total retention at these time intervals of 24.71, 26.59 and 26.06 per cent of the administered dose.

Additional observations on the relationship of xanthopterin to folic acid. LEMUEL D. WRIGHT (by invitation), HELEN R. SKEGGS (by invitation) and ARNOLD D. WELCH. *Nutritional Labs., Dept. of Pharmacology, Medical-Research Division, Sharp and Dohme, Inc., Glenolden, Pa.* It has been reported previously that the observed folic acid content of incubated rat liver tissue may be increased several fold by the presence of xanthopterin. A more comprehensive study of the effect of various experimental procedures on the observed folic acid content of rat liver and muscle has now been conducted.

The observed folic acid content of incubated rat liver is influenced by such factors as the degree of dispersion of the tissue, nature of the incubation medium, presence of digestive enzymes, pH, amount of neutral salt present, cyanide, and xanthopterin. The data suggest that free folic acid in rat liver is convertible by liver enzymes to a material having little or no microbiological activity. The reaction is inhibited by: (1) neutral salts in moderate amounts (larger amounts apparently inhibit the enzymatic release of combined folic acid), (2) allowing the liver to incubate in fragments rather than in a finely dispersed form, and (3) the presence of xanthopterin. In rat skeletal muscle disappearance of folic acid could not be demonstrated and xanthopterin did not influence the observed folic acid content of the muscle.

Although the formation of folic acid from xanthopterin has not been excluded the data suggest the involvement of a metabolite-antimetabolite relationship or mass action inhibition of enzymatic activity. The observation that folic acid may undergo destruction or modification in the liver (and possibly in other tissues and natural materials as well) may be of aid in the interpretation of certain phases of folic acid metabolism.

Pharmacologic localization. FREDRICK F. YONKMAN and BARBARA R. RENNICK (by invitation). *Wayne Univ. College of Medicine, Detroit, Mich.* Of the numerous procedures employed in localizing pharmacologic action several are of greater application than are others. One of these is the technique utilized by several investigators in which

one or more functions of the cervical sympathetic nerve are studied under the influence of drugs. By this means we have studied ipsilateral sympathetic salivation, mydriasis and contraction of the nictitating membrane in cats anesthetized with urethane or ether. Concomitant effects on blood pressure were also observed. Drugs investigated with this procedure included among others: 2-naphthyl-methyl imidazoline (Privine-Ciba), β-diethyl-aminoethyl diphenylacetate (Trasentin-Ciba), and some new antispasmodics (S-Compounds) of morpholine derivation (Parke Davis). The following results, gained from intravenous administration of varying dosage on a per kg. basis, are significant:

a. Privine, 0.1 mgm. produced no salivation of sympathetic origin despite a tension rise which was comparable to that effected by 0.01 mgm. of epinephrine. The latter drug invariably produced salivation.

b. Privine, 1.0 mgm. produced salivary secretion which was cholinergically induced since this effect was nullified by atropine.

c. Privine, 0.1 mgm. or more, almost invariably caused maximum constriction of the nictitating membrane. This effect was due apparently to cholinergic as well as adrenergic augmentation since both atropine and ethyl yohimbine had marked, although individually incomplete, lytic effects in this situation. The morpholine-derivatives, S-28 (β,β-dimethyl-γ-4-morpholinepropyl-diphenylacetate HCl) and S-29 (ω-4-morpholine-hexyl diphenylacetate HCl) in 10–40 mgm. doses had no lytic effect in this contractile state, but Trasentin was slightly lytic following Privine.

d. The morpholine derivatives, 10–40 mgm. and Trasentin, 10 mgm., had no antisalivary effect, regardless of how salication had been augmented.

e. Pupillary reactions to Privine were too variable to lend themselves to adequate quantitation at present but frequently mydriasis resulted.

f. The S-compounds had some acutely hypotensive effects but less so than that effected by Trasentin in comparable dosage.

Thus, it seems that Privine has a dual action, cholinergic and adrenergic, in relation to some cervically controlled end organs; Trasentin has some anticholinergic action whereas the morpholine derivatives S-28 and S-29, exhibit no significant anticholinergic action in the large doses employed.

THE AMERICAN SOCIETY FOR EXPERIMENTAL PATHOLOGY

Abstracts of papers received from the Secretary of the Society. Since there will be no meeting in 1944 these papers are to be regarded as "read by title". For possible corrections in any of these abstracts see the next issue.

Acute anemia of tumors. FREDERICK M. ALLEN. *City Hospital, New York.* Previous studies on general effects of tourniquets were extended to include tumors. (Arch. Surg. **41**: 79, 1940). Total deprivation of blood for periods of 6 to 12 hours always damages tumors more than the normal tissues. Without necrosis in the normal tissues, the necrosis of the tumors may range from partial to complete. The effects differ with different kinds of tumors and particularly with different animal species, but there is no regular distinction between native and artificially transplanted tumors. Evidence indicates that the tumor death is due not directly to the asphysia but to an influence of the inflammatory reaction.

The previous clinical report included one cure of a squamous cell carcinoma of the face. After long delay, there has been opportunity to test a few more cases in the City Hospital. One squamous cell carcinoma of the leg was cured. Most of the nodules of a Kaposi sarcoma were apparently cleared up, but the patient's death from pneumonia cut short the observations. One keloid was cured as far as brief observation can decide. Further trials, especially with tumors of higher malignancy, are urgently needed before any conclusions can be drawn. The method, if unsuccessful, is not adapted to very wide practical application but may have considerable theoretical interest.

Relative utilization of ferrous and ferric radioactive iron in clinical and experimental anemia. P. F. HAHN, R. C. LOWE (by invitation), G. R. MENEELY (by invitation) and W. F. BALE (by invitation). *Depts. of Biochemistry and Medicine, Vanderbilt Univ. School of Medicine, Dept. of Medicine, Louisiana State Univ. Medical School, and the Depts. of Pathology and Radiology, Univ. of Rochester School of Medicine.* Six patients diagnosed as having hypochromic anemia of iron deficiency were fed 10 mgm. test doses of ferrous sulphate and ferric ammonium citrate tagged with the radioactive isotope of iron. In some instances

the ferrous salt was administered first and blood samples taken on the fourth, sixth, and eighth days after feeding. The ferric salt was then fed at the same dosage level with sampling at similar intervals. Finally the ferrous salt was again fed and blood taken at the same intervals. In the other patients the order of administration of the salts was reversed. By means of the concentration of the tagged iron in the circulating red cells and an estimation of the circulating red blood cell mass, the fraction of the fed iron absorbed and utilised for hemoglobin formation was determined. In about half the instances the ferrous iron was taken up to about twice the extent of the ferric iron and in the other half there was no noticeable difference in utilization. In no instance was there more ferric iron utilised than ferrous iron.

In three dogs depleted of their iron reserve stores by long continued chronic hemorrhage four similar experiments were carried out under better controlled conditions. In each instance the ferrous iron was utilized from two to four times as completely as the ferric salt. In the experiments conducted on dogs the ferric and ferous chorides were the salts compared. The ferrous salts in all cases were formed from the corresponding ferric salt either by the addition of sufficient cevitamic acid to cause reduction, or by passing a stream of sulfur dioxide through the solution. The reduction method used seemed to have no effect on the results.

Under the conditions of this experimental approach it appears that ferrous iron salts are more efficiently handled than ferric salts in iron deficiency anemia.

Lymphopenia and atrophy of lymphatic tissue associated with acute renal insufficiency in adult dogs. RUSSELL L. HOLMAN. *Dept. of Pathology, Univ. of North Carolina, Chapel Hill.* During studies on the relation of diet and renal insufficiency to arterial disease in dogs necropsy studies revealed gross and histological changes interpreted as "exhaustion atrophy" in all the lymphatic tissues studied (spleen, thymus, mesenteric and popliteal lymph nodes, Peyer's patches, and solitary follicles). These changes consisted of a general "washing out" of lymphocytes and a curious regressive change in the "germinal centers" that seems best described by the term "reticular arrest," for the cells that constitute the remnants of the "follicles" look like reticular cells and silver stains are consistent with this interpretation. Gross weights of the spleen and popliteal lymph nodes in these dogs averaged less than half the weights of the corresponding lymphatic tissues in control dogs, and lymphocyte counts of the circulating blood showed an average reduction to 32 per cent of the control level.

The only known factor common to all the dogs that have shown these atrophic changes was acute renal insufficiency. These changes were independent of diet and the method by which renal insufficiency was produced (uranium nitrate, mercuric chloride, or bilateral nephrectomy). They have been observed as early as four days after renal injury, and the evidence in dogs that survived the acute renal injury indicated that they are reversible.

Control data militate against any of the known indirect actions of renal injury such as inanition, acidosis, and infection. The suggestion of hormonal activity (lymphocyte maturation factor?) by the renal cortex is offered, but many other explanations are possible. [*This work was aided by a grant from The John and Mary R. Markle Foundation.*]

Electrocardiographic changes in uremia associated with a high concentration of serum potassium. Report of three cases. NORMAN M. KEITH, HOWARD B. BURCHELL (by invitation) and ARCHIE H. BAGGENSTOSS (by invitation). *Mayo Clinic, Rochester, Minn.* Previously the authors demonstrated that defects of intraventricular conduction developed in the electrocardiograms of two patients who suffered from uremia and had an abnormal increase in the concentration of potassium in the serum. Subsequently, a third patient was observed for a period of six weeks. In this period this patient passed through different phases of uremia. During the terminal phase the serum potassium increased rapidly and an intraventricular defect developed in the electrocardiogram. This study includes data on the clinical course, pathologic findings, on renal function and on the chemistry of the blood and significance of the electrocardiographic tracings of these three patients.

Different pathologic lesions were found in the kidneys of each patient. The lesions were chronic glomerulonephritis, chronic bilateral hydronephrosis and pyelonephritis, and passive congestion, respectively. Intraventricular block developed both with and without pericarditis, and with and without histopathologic lesions in the myocardium. It was present when the concentration of serum potassium varied from 8.7 to 10.4 milli-equivalents. The concentrations of potassium encountered were lower than those noted by others when similar electrocardiographic changes were observed in the dog and cat. The marked alterations in many of the constituents of human blood serum may account for this difference.

Observations on these three patients support the hypothesis that cardiac death was due to potassium toxemia. If subsequent findings confirm this hypothesis, it seems clear that a disturbance in the electrolytic balance in blood serum of uremic patients can cause a fatal upset in the

cellular metabolism of a vital organ, in this instance, the heart.

Effect of local irritant on skin of dogs: influence of fat in diet. JENNINGS KOODA (by invitation), ARILD E. HANSEN and M. G. FREDRICKS (by invitation). *Dept. of Pediatrics and the Division of Dermatology and Syphilology of the Univ. of Minnesota, Minneapolis and the Dept. of Pediatrics of the Univ. of Texas Medical School, Galveston.* The purpose of this study was to determine the effect of fat in the diet on the ability of the skin of dogs to resist local irritation. Each day for a period of 6 weeks a 3 per cent solution of croton oil in acetone was applied to comparable areas on the dorsum of 2 young litter mate dogs. One animal received a diet low in fat (0.16 per cent) and showed the generalized flaky desquamation described by Hansen and Wiese; the other animal received the same diet except for the substitution of 28 per cent of the sucrose calories by fresh lard and had no abnormality of the skin. By 2 weeks the treated area on the animal on the low fat diet showed a definite erythema, some thickening, papules, and vesicles with exudation and crusting. These changes, maximum in intensity after 3–4 weeks, remained the same as long as the irritating preparation was applied. The comparable region on the animal having fat in the diet at first showed slight erythema with a few papules but this eruption subsided by 4 weeks and during the last 2 weeks the skin remained practically clear. Histologic sections of the skin biopsied at the end of the 6 week period from comparable sites were stained with hematoxylin and eosin. The section from the animal on the low fat diet showed foci of infiltrate of lymphocytes and disintegrating polymorphonuclear leukocytes localized about the hair follicles in the pars papillaris of the corium. The rete of the epidermis was thickened, clusters of exudate were noted on its surface and over some of the foci; the epidermis was thin, fragmented and invaded by the infiltrate. In the section from the animal receiving lard, an infiltrate, similarly situated but much less marked, consisted of lymphocytes with a few polymorphonuclear leukocytes. The findings described in the epidermis of the other animal were not present in this section. The above experiment has been repeated with the same 2 dogs after a lapse of 8 weeks with similar observations regarding the gross appearance of the skin. [*Aided by grants from the National Live Stock and Meat Board through the National Research Council and Medical Graduate Research Fund of the University of Minnesota.*]

Hepatic necrosis and other lesions produced in rats by feeding quinacrine (Atabrine). ARTHUR A. NELSON and O. GARTH FITZHUGH (by invitation). *Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington, D. C.* With one exception (Wright and Lillie, Pub. Health Repts. **58**: 1242, 1943), there have been reported no severe pathological lesions produced experimentally by quinacrine (Atabrine). Twenty-one day old albino rats fed 800 ppm. of quinacrine in a low protein diet regularly showed, after 5 to 20 weeks, necrosis of half or more of the liver, hyperplasia and/or atrophy of the viable hepatic cells, hepatic thrombosis, peritoneal adhesions, atrophy of the testis, relative enlargement of the spleen, and hyperplasia of the bone marrow. Small basophilic granules of a type never seen in previous experimental animals were present in several locations, as were foamy macrophages with or without similar basophilic granules. On a high protein diet the same dose of quinacrine was lethal in about 30 weeks, with less hepatic and more cardiac damage, including frequent thrombosis of the left atrium. With half or less of the above dose of quinacrine, lesions were present but were sharply reduced in severity. The above report confirms that of Wright and Lillie.

Absorption of vitamin A in the rat intestine. HANS POPPER and BRUNO W. VOLK (by invitation). *Hektoen Inst. for Medical Research of the Cook County Hospital, Chicago, Ill.* The absorption of vitamin A in the rat intestine was investigated by fluorescence microscopy and compared with that of the histologically demonstrable fat. On 10 different levels of the gastrointestinal tract sections of the wall and smears of the content were examined. In starving rats or after feeding of corn oil or lard no vitamin A was demonstrable in them. After feeding of vitamin A in oil, it was found in the lumen only down to the level of the lower duodenum, even if up to 400,000 units were administered. In the villi and lymphatics of the wall it was seen down to the end of the small intestine, the peak of absorption being on the border between its upper and middle third. The maximal fat absorption occurred on the same level, although fat was demonstrable in the content of the entire intestine.

Simultaneous administration of vitamin E did not influence the picture of vitamin A absorption. Administration of atropine decreased the vitamin A absorption; it was seen in the lumen of the entire small intestine. Excretion of intact vitamin A in the feces seems, therefore, not to explain the known incomplete utilization of fed vitamin A. It is concluded that the vitamin A absorption decreases in the lower intestine because the nonabsorbed vitamin A has been destroyed or because its greater part has already been absorbed. Both possibilities suggest an extensive destruction of vitamin A either in the intestinal lumen or after absorption in the organism.

Salt metabolism in poliomyelitis. JAMES F. RINEHART. *Univ. of California Medical School,*

San Francisco. Although the virus of poliomyelitis is probably widely disseminated during epidemic periods, relatively few develop the disease. This and other epidemiologic considerations suggest that there is some predisposing factor in the host which increases his susceptibility to poliomyelitis. Studies of patients during the recent epidemic reveal the frequent occurrence of salt depletion and hemoconcentration early in the course of the illness. The average whole blood chloride concentration in 30 cases, examined during the first week, was 457 mgm./100 cc. The spinal fluid chloride concentration in 30 cases averaged 690 mgm./100 cc. The average packed cell volume in children was 42.5% (32 cases), in women 44% (11 cases), and in men 48% (6 cases). In 14 cases observations were made early in the illness and again from one to two weeks later. In 12 of the 14 cases the chloride concentration was found elevated and in 10 cases the packed cell volume was lowered on the second determination. In 5 cases studied during the first 4 days of illness there was significant retention of chloride demonstrated in balance studies of cases given supplementary salt.

It is suggested that salt depletion due to loss through sweating and concurrent hemoconcentration may be factors predisposing to virus invasion and the development of the disease. The decided summer incidence of poliomyelitis, the apparent predisposition of the active robust child, and the reputed association of the disease with antecedent strenuous physical activity are epidemiologic considerations which appear to be in harmony with the concept. Further clinical investigation and appropriate anim[illegible] studies in this field are clearly indicated. Attention to salt and water metabolism would appear desirable in the management of cases.

Protection of the vitamin A fluorescence in tissue sections by biologic media. BRUNO W. VOLK (by invitation) and HANS POPPER. *Hektoen Inst. for Medical Research of the Cook County Hospital, Chicago, Ill.* If frozen sections of human or animal organs containing vitamin A were kept in water or saline solution, their vitamin A fluorescence decreased and disappeared within 48 hours. The fluorescence disappeared faster from animal than from human organs and remained longer in the liver cells than in the Kupffer cells. Addition of hydrogen peroxide accelerated the disappearance of the fluorescence considerably. If the sections were kept in human plasma or serum, the disappearance of the fluorescence was markedly delayed. Thin emulsions of liver delayed the disappearance of the fluorescence slightly less, emulsions of kidney, spleen, thyroid, and pancreas, furthermore urine, bile, spinal and ascitic fluid and suspensions of leucocyte and various bacteria were markedly less effective. Emulsions of myocardium and pulmonary tissue delayed the disappearance of the vitamin A fluorescence only slightly.

This protective ability of the human plasma was not significantly reduced by heating, ether extraction, tryptic digestion or moderate putrefaction. It was found in plasma dilutions up to 1:32. The titer varied in different patients and did not depend upon the vitamin A concentration in the plasma. The titer seemed to increase after food intake.

Whether this principle which is found in biological material and which protects the vitamin A fluorescence of tissue sections in vitro, has biological significance in the protection of the vitamin A stores in vivo, is not established.

THE AMERICAN INSTITUTE OF NUTRITION

Abstracts of papers received from the Secretary of the Society. Since there will be no meeting in 1944 these papers are to be regarded as "read by title". For possible corrections in any of these abstracts see the next issue.

Effect of protein quality in production of dietary cirrhosis of the liver in rats. HAROLD BLUMBERG and E. V. MCCOLLUM. *Dept. of Biochemistry, School of Hygiene and Public Health, Johns Hopkins Univ., Baltimore.* When purified diets have been employed for producing dietary cirrhosis of the liver in rats, the diets have been ordinarily considered as choline-deficient and low in protein. However, the protein used has been casein, which is high in methionine and low in cystine.

The effect of protein quality was investigated by comparing casein (high-methionine, low-cystine, arachin (low-methionine, medium-cystine), and glycinin (medium-methionine, medium-cystine). The following diet was used: protein 20.0, sucrose (or dextrin) 64.0, lard 9.0, salts 6.0, and oleum percomorphum 0.06 per cent, plus alpha-tocopherol, thiamine, riboflavin, pyridoxine, calcium pantothenate, and nicotinic acid.

Each group consisted of 6 young rats. The casein

rats grew well, had good fur, and had essentially normal livers when the experiment was terminated after 7 months. The arachin rats scarcely grew, were in poor condition, had partial alopecia, and had very fatty livers with occasional slight fibrosis, but not cirrhosis. The glycinin rats made slow initial weight gains, were in fair condition, and had moderately good fur. The livers were moderately fatty, and cirrhosis was present in all animals except one which died early.

The therapeutic value of improving protein quality was indicated by apparent arrest of the cirrhotic process upon changing an animal, long maintained on glycinin, to the casein diet.

The production of cirrhosis on a choline-deficient diet quantitatively adequate in protein, i.e., 20 per cent glycinin, illustrates that cirrhosis in the rat is not necessarily associated with "low protein" diets. Protein quality, as well as protein quantity should be remembered in considering diet and cirrhosis. [*This investigation was aided by a grant from the Josiah Macy, Jr. Foundation.*]

The effects of hexoses on the respiratory quotients of cats. THORNE M. CARPENTER. *Nutrition Lab., Carnegie Inst. of Washington, Boston, Mass.* Respiratory quotients (R. Q.) were determined by the open-circuit method for 8 successive half-hour periods with 1 female and 6 male cats (2.8 to 4.5 kgm.) in the fasting condition (29 experiments), after 75 cc. of water (25 experiments), and after ingestion by stomach tube of 10 grams each of glucose (30 experiments), fructose (29 experiments), and galactose (24 experiments). The average fasting R. Q.'s of these cats ranged from 0.76 to 0.78. Ingestion of water produced a slight increase in R. Q. for 2 to 2½ hours. Glucose produced a marked increase, with an average maximum of 0.90 in the seventh half hour. Ingestion of fructose was followed by an average rise to 0.84 in the fifth half hour. Galactose produced about the same rise as fructose and in the same time. The cats differed from one another in their responses to sugar ingestion, as shown by the ranges in their average R. Q.'s for 4 hours. After glucose ingestion the range was from 0.82 to 0.91, after fructose 0.79 to 0.85, and after galactose 0.79 to 0.88. The effect of 10 grams of any one of these sugars lasts longer than 4 hours, as shown by 5 experiments with 2 cats in which basal values were not reached during 7½ hours. The findings with the cats resemble those with man after glucose ingestion but differ considerably from those with man after fructose and galactose, as both these sugars produce an early, marked rise with man.

Carbohydrate metabolism in vitamin B_1 deficiency. ANNETTE CHESLER (by invitation), EDMUND HOMBURGER (by invitation) and HAROLD E. HIMWICH. *Dept. of Physiology and Pharmacology, Albany Medical College, Union Univ., Albany, N. Y.* In order to study the biochemical changes occurring in vitamin B_1 deficiency, 16 dogs were placed upon a synthetic diet, vitamin free, to which was added synthesized members of the vitamin B complex, C and K, and vitamins A and D concentrate. After 3½ months these animals were injected intravenously with glucose, 2 gm. per kilo and pyruvic acid, 0.5 gm. per kilo, to establish the control tolerance curves. In each instance glucose, lactic acid, and pyruvic acid were determined.

Ten of the animals were then placed on the same diet as before except devoid of vitamin B_1, while 6 animals were retained as controls. Before the 10 deficient animals exhibited signs of avitaminosis, they were again studied. Abnormally high concentrations of glucose, lactic acid, and pyruvic acid were observed.

The third set of observations were performed on seven animals in extremis. All showed abnormally high glucose, lactic acid and pyruvic acid blood values both post-absorptively and following the injection of either glucose or pyruvic acid. In the first set of observations the lactic acid/pyruvic acid ratio was 7.7. In the partially deficient animals the ratio averaged 6.2, while in extremis the ratio was 10.7. Histologic examination of the tissues of these animals is now in progress as well as biochemical and histological studies of animals maintained in a state of chronic deficiency for about 6 months. [*Aided by a grant from the Williams-Waterman Fund of Research Corporation.*]

Associative dynamic effects of protein, carbohydrate and fat. E. B. FORBES and R. W. SWIFT (with the technical collaboration of Ann G. Buckman), JANE E. SCHOPFER and MARY T. DAVENPORT. *Inst. of Animal Nutrition, School of Agriculture, Pennsylvania State College.* A study was made, with mature albino rats as subjects, of the dynamic effects of beef muscle protein, cerelose (corn sugar) and lard, individually and in four combinations, as supplements to a complete basal diet sufficient for maintenance.

The individual supplements each increased heat production from its own kind of nutriment. Carbohydrate and protein each spared the other two kinds of nutriment, while fat spared only protein.

The sparing effects of the mixed supplements depended on their composition, but all spared fat.

In the mixed supplements fat was much more potent than were protein and carbohydrate in determining dynamic effects.

The supplement of protein and fat had the lowest dynamic effect of all, lower even than that of fat; while the combination with the highest dynamic effect was that of carbohydrate and protein.

The observed dynamic effect of carbohydrate and protein was 12.5 per cent less, of carbohydrate

and fat 35 per cent less, of protein and fat 54 per cent less, and of carbohydrate, protein and fat 22 per cent less, than as computed from experimentally determined values for the individual nutrients.

The idea that the dynamic effects of diets vary in the order of their protein contents was found incorrect; and inasmuch as there is no scientific means of apportioning energy effects or values among dietary constituents, the dynamic effects of individual foods or nutrients are without significance as constants.

Effect of addition of lard to a low fat diet in dogs. ARILD E. HANSEN, HILDA F. WIESE (by invitation) and ERMA V.O. MILLER (by invitation). *Dept. of Pediatrics, Univ. of Minnesota, Minneapolis, and Dept. of Pediatrics, Univ. of Texas Medical School, Galveston.* This study concerns two dogs from a total of nine puppies which were maintained on a diet low in fat (0.13%). These animals developed a characteristic flaky desquamation of the skin with dry coarse hair and analysis of the blood serum showed the average values for the blood lipids (including cholesterol, cholesterol esters, total fatty acids, acetone soluble, and acetone insoluble fatty acids as well as the iodine numbers of the fatty acids) to be in the same range as those previously reported by the authors. Subsequently one animal was given fat in the form of fresh lard to the extent of 28% of its calories. Ten days after lard was added to the diet, there was a rise in the iodine number of the fatty acids in the serum, although the amount of fatty acid remained practically the same. There was no noticeable change in the character of the skin and hair at this time. Two weeks later there was a definite improvement in the appearance of the skin characterized by a peeling of the outer layers of epidermis and the formation of new soft skin. By this time the iodine number of the acetone soluble fatty acids rose from 85 to 122 and of the phospholipid fatty acids from 96 to 109. There was still no appreciable increase in the amount of fat in the serum. As regards the second animal which was given lard to the extent of 5% of the total calories, no definite improvement in the appearance of the skin was evident until one month after lard was added to the diet. At the 5% level, the iodine value of the acetone soluble fatty acids rose more slowly from an average of 87 to 103 in 4 weeks and to 108 by six weeks. The iodine number of the phospholipid fatty acids remained the same for 4 weeks but increased slightly from 102 to 107 by six weeks. [*This study was made possible by a grant from the National Live Stock and Meat Board through the National Research Council.*]

The effect of atabrine on thiamin deficiency in young rats. D. M. HEGSTED (by invitation), J. M. MCKIBBIN (by invitation) and F. J. STARE. *Division of Nutrition, Dept. of Biochemistry, Schools of Medicine and Public Health, Harvard Univ., Boston.* Previous investigations upon the effect of atabrine administration to rats on various dietary regimes have shown that on a choline deficient ration the addition of 40 to 65 mg. per cent of atabrine prevented death and almost abolished gross signs of kidney disease. Similar studies using a thiamin deficient ration have shown that atabrine has a "thiamin sparing" action.

Comparable groups of young rats have been fed a purified ration lacking in thiamin. Atabrine, 40 mg. per 100 grams of ration, was added to the diet of half of the animals. Food intake of the controls (no atabrine) was limited to that of the atabrine groups during the depletion period. The animals receiving no atabrine reached a maximum weight in ten days, lost weight rapidly, and died on the twenty-eighth day (average). Animals receiving atabrine continued to gain until the fifteenth day and then lost weight very slowly. They did not die until the forty-eighth day (average).

In a similar experiment small supplements of thiamin, 3 mcg. per day, were given after the depletion period. The animals receiving atabrine gained more per day (1.78 grams) than did the control animals (1.20 grams) even though the animals receiving atabrine had been on the thiamin free ration for eight days longer than the controls.

Fluorine is necessary in the diet of the rat. J. F. MCCLENDON. *Hahnemann Medical College and the experimental farm of J. F. McClendon.* A fluorine-free diet was prepared from food grown in solution culture and chemically pure substances in grams (dry) as follows: 500 yellow corn, 300 glucose, 50 years, 19 soy beans, 20 bean and corn leaves, 1 lysine, 10 NaCl, 80 corn oil and 20 cod liver oil. Two rats (whose mother's diet contained 0.3 parts of fluorine per million) were put on the fluorine-free diet at the age of 21 days. One rat died of starvation in 48 days because caries had destroyed the effective chewing surfaces of all of the molar teeth, and it stopped eating. The other rat was saved from starvation with 10 cc. of milk containing 1 microgram of fluorine, but died of starvation in 70 days. The crowns of the 12 molar teeth of each rat were practically removed by caries except that the caries of the 3rd molars (which are of little use in chewing) was less extensive. This is the most extensive caries seen in any rat on any diet for any number of days. This production of 12 carious teeth per rat in 48 and 70 days may be compared with 0.3 carious teeth per rat in 40 days and 3 carious teeth per rat in 75 days on a diet which was apparently not superior except that it contained 0.3 parts of fluorine per million, and no caries in 75 days when 10 parts of fluorine

per million was added to the drinking water. Fluorine is necessary in a diet that has to be chewed.

Choline deficiency studies in dogs. J. M. McKIBBIN (by invitation), S. THAYER (by invitation) and F. J. STARE. *Division of Nutrition, Dept. of Biochemistry, Schools of Medicine and Public Health, Harvard Univ., Boston.* Weanling puppies were placed on a ration consisting of sucrose 49.5, alcohol and ether extracted peanut meal 30, cottonseed oil 7, cod liver oil 3, salts 4, casein 6, and K_2HPO_4 0.5. Supplements of thiamin chloride, pyridoxine hydrochloride, riboflavin, calcium pantothenate, and nicotinic acid were added to the ration. Control animals received 200 mg. per cent of choline chloride. Both control and deficient animals grew poorly on this ration, and four of the six dogs died within 38 days.

Another litter of five puppies received a similar ration but modified as follows: casein 7, cod liver oil 2, and liver extract 2. Two dogs not receiving choline died within two weeks and on necropsy showed extremely fatty livers. The controls grew normally for 18 to 20 days then rapidly lost weight and died by the twenty-fifth day. These animals had normal livers but showed engorgement of kidneys, intestines, pancreas, and hemorrhages into the kidney medulla.

Three litters totaling 12 puppies were then placed on the modified ration but containing 3 per cent of a different liver extract. Six control animals received choline, and one control received 0.7 per cent methionine without choline. Growth in the control animals was retarded somewhat at first but became normal after the third week. The deficient dogs failed to grow and at necropsy on the thirty-second to forty-third days showed extremely fatty livers, whereas the controls appeared grossly normal. Prothrombin time, bromsulfalein test, and serum phosphatase indicated severe liver disease in the deficient but were normal in the controls.

Effect of protein deficiency on plasma protein and plasma volume. JACK METCOFF (by invitation), C. B. FAVOUR (by invitation) and F. J. STARE. *Division of Nutrition, Dept. of Biochemistry, Schools of Medicine and Public Health, Harvard Univ., and Medical Clinic of the Peter Bent Brigham Hospital, Boston.* Weanling rats were placed on a purified diet containing sucrose, corn oil, salts, crystalline B-vitamins, and "vitamin-free" casein at an 18 per cent level. Vitamins A and D were furnished by Haliver oil fed biweekly. After one week of growth on this diet, total protein, hemoglobin and hematocrit determinations were made. The rats were divided into two groups and in one of these the casein level was decreased to 8 per cent. After three weeks the control group had more than trebled its initial mean body weight increasing at a mean growth rate of approximately 3.0 grams a day. The group on the low casein diet grew poorly, increasing at a mean growth rate of approximately 1.0 gram a day. At this time, total protein, hemoglobin, and hematocrit determinations were repeated, and, in addition, plasma volume was measured.

Although growth was markedly diminished in the deficient animals, their total proteins, hemoglobins, and hematocrit values had apparently increased and were essentially the same as those of the controls. The total plasma protein concentration, however, was significantly altered; mean plasma volume per 100 gram body weight in the control group being approximately 30 per cent greater than that of the experimental group.

In view of the concept of dynamic equilibrium, presumably the protein deficient rat at 3 weeks maintains the plasma protein level by a decrease in plasma volume and failure of tissue growth. Work now in progress is concerned with the possible relationship between these phenomena and susceptibility to infection.

The hematopoietic value of certain dietary proteins in the hemorrhagic anemia of the rat. JAMES M. ORTEN and ALINE UNDERHILL ORTEN (by invitation). *Dept. of Physiological Chemistry, Wayne Univ., College of Medicine, Detroit.* Hemorrhagic anemia was produced in adult rats by the removal of 30% of the calculated blood volume (2.0 cc. per 100 gram body weight) from the warm, oiled tail. An equal volume of 0.9% physiological saline, for fluid replacement, was injected intraperitoneally immediately after the bleeding. This method has proved highly satisfactory.

Rats were fed from weaning adequate synthetic diets containing 18% of the protein to be studied. Animals given lactalbumin regenerated hemoglobin to the pre-hemorrhage level in an average of 18 days. Approximately 90 mg. hemoglobin per rat per day, or 18 mg. per 100 gram body weight, and 39 mg. per gram of protein ingested per day were regenerated during the 18-day period. Similar values were obtained when the protein was supplied as either casein, skim milk solids, or a skim milk-blood solids mixture.

Paradoxically, with dried beef blood as the protein, 21 days were required for hemoglobin regeneration. Only 16 mg. hemoglobin per rat or 17 mg. per 100 gram body weight, and only 17 mg. hemoblobin per gram of dietary protein were formed per day.

With a low level of lactalbumin (2.8% protein), 28 days were required for the hemoglobin value to return to the prehemorrhage level and only 9 mgm. hemoglobin per day or 11 mg. per 100 gram body weight per day were formed. However, approximately 75 mg. of hemoglobin were formed daily for each gram of protein ingested.

These data emphasize the importance of both

the quality and quantity of dietary protein in hemoglobin formation.

The utilization of thiamine from four yeasts. HELEN PARSONS, AUDREY FOESTE (by invitation), ANNE WILLIAMSON (by invitation) and HULDA STETTLER (by invitation). *Dept. of Home Economics, Univ. of Wisconsin, Madison.* The utilization of thiamine from four types of moist yeast was determined by means of growth in rats and thiamine elimination by human subjects. The yeasts were fed both fresh and after treatment (boiling or soaking in alcohol, aimed at injuring the protoplasmic membrane) at the equivalent of 4 μg. thiamine per rat and 2 to 3.7 mg. per person per day.

Three of the four types of yeast, only moderately enriched, each yielding 0.5 mg. thiamine per cake were all less well utilized, judged by the criteria mentioned, when fed fresh than after treatment; in fact, the urinary thiamine on the fresh yeasts was not raised above that on the basal diet alone.

These results confirmed earlier published reports from this laboratory on two of these brands (A and B). The third (C) of this comparable group had as a control a heavily enriched brand (D) yielding 3.7 mg. thiamine per cake but otherwise identical with Type C. In tests with both human subjects and animals fed Type D at the same thiamine levels as before, this proved to be the only one of the four yeasts which was approximately equally well utilized in the fresh and treated forms. It is therefore concluded that its superior utilization in the fresh state in comparison with the other three types is not attributable to the strain of yeast but to the comparatively high proportion of thiamine to yeast cells, thus probably accounting for the greater availability of its thiamine for absorption.

Choline as an adjuvant to the dietary therapy of clinical cirrhosis of the liver. A. H. RUSSAKOFF (by invitation) and HAROLD BLUMBERG. *Medical Service, Sinai Hospital and Dept. of Biochemistry, School of Hygiene and Public Health, Johns Hopkins Univ., Baltimore.* The effect of dietary therapy was studied in nine patients with clinical evidence of decompensated portal cirrhosis of the liver. In addition to high protein, high carbohydrate, low fat, high vitamin diets (P 125–150, C 300, F 50–60 grams), supplements of choline chloride were administered orally in doses up to six grams daily (two grams thrice daily). Seven of the nine patients showed definite improvement, as evidenced by clinical and laboratory findings. Generally, the enlarged livers were considerable reduced in size, ascites was greatly diminished or disappeared, serum proteins (albumin) increased, the hemogram improved, the prothrombin time decreased, and liver function tests became normal. Two patients failed to improve. One had an enlarged fibrotic, but non-fatty liver (autopsy); the other had a small shrunken liver.

Noteworthy were three patients who showed no improvement when first treated for three weeks with the adopted high protein diet alone. In all three cases, improvement was noted within the first ten days of choline therapy. Improvement continued, and the patients were discharged within two months.

The development of clinical cirrhosis, particularly in alcoholics, is frequently associated with hepatic infiltration by neutral fat, that form of lipid upon which choline has a highly effective lipotropic action. In experimental animals, choline has a beneficial effect in the prevention and treatment of several types of dietary cirrhosis. This preliminary investigation suggests that in some cases choline may provide an important adjuvant to the therapy of clinical cirrhosis of the liver. [*Acknowledgment is made to the Edwin B. Hutzler Research Fund of Sinai Hospital for the choline chloride used in this study.*]

Evidence for a new B-complex factor in yeast concerned with hemoglobin production in the dog. SUSAN GOWER SMITH. *Dept. of Medicine, Duke Univ. School of Medicine, Durham, N. C.* It has been observed that puppies on a synthetic diet containing Brewer's yeast at a level of 10% will regularly elevate their hemoglobin to 18–20 grams and maintain it at this level for an experimental period of 1–2 years in spite of the fact that the accepted normal hemoglobin for the dog is 14 grams. Litter mates of these animals on a synthetic diet of the same ingredients except for the yeast and supplemented with eight synthetic vitamins (vitamins B_1 and B_2, riboflavin, nicotinic acid, pantothenic acid, inositol, para-aminobenzoic acid, choline) fail to gain weight at the normal rate; and although their hemoglobin usually reaches 18 grams at some point in the curve, they cannot maintain it at this level. It drops gradually to 10 grams or below, and the anemia produced tends to be normocytic in contrast to the hypochromic, microcytic anemia observed when vitamin B_6 is lacking.

Since the eight synthetic factors given are inadequate to maintain the dogs' hemoglobin at optimal or normal values, and since the factor concerned is found in a water soluble fraction of the yeast, it is probably among the unknown or known but unsynthesized members of the B complex. The three most likely factors are folic acid, xanthopterin and vitamin B_c, all of which have been associated with hematological changes. Folic acid and xanthopterin have been tested and failed to give a positive response. It is probable, then, that the factor concerned is a new member of the vitamin B-complex.

Nutritional adequacy of human plasma protein

. J. Stare, D. M. Hegsted (by invitation) and . M. McKibbin (by invitation). *Division of utrition, Dept. of Biochemistry, Schools of Medine and Public Health, Harvard Univ., Boston.* Weanling rats were fed a purified diet of sucrose, orn oil, salts, crystalline B-vitamins, and dried uman plasma. The plasma was added at a level supply 18 per cent protein in the diet. Vitamins and D were supplied by Haliver oil given twice eekly. Control animals received a diet of idential composition except that the protein was furished by "vitamin-free" casein. Growth and eneral appearance of the animals on the casein ation were greatly superior to those on the plasma ation; the former averaged a daily gain of 3.3 rams, the latter of 0.9. In subsequent experiments mino acid supplements were made to the plasma ation; the plasma content was decreased sufficiently to maintain a nitrogen content comparable the previous experiments. Of the amino acids dded (isoleucine, leucine, valine, tryptophane, ethionine, arginine) dl isoleucine produced the reatest effect, and provided growth nearly quivalent to the simultaneous addition of all x. A typical experiment showed the following eight gains (grams per day): casein, 3.0; plasma, 1; plasma plus 0.5 per cent dl isoleucine, 2.4. hus when the nutritional adequacy of the proins of human blood plasma is measured by the t growth method, isoleucine appears to be the rincipal essential amino acid lacking in the diet.

Distribution of fatty acids in the blood serum of ogs as affected by diet. Hilda F. Wiese (by invitation) and Arild E. Hansen. *Dept. of Pediatrics, Univ. of Minnesota, Minneapolis, and Dept. f Pediatrics, Univ. of Texas Medical School, alveston.* A study has been made of the distribuon of the fatty acids (with special reference to eir degree of unsaturation) in the blood serum f 2 groups of dogs. In one group, 5 young dogs ere maintained on a diet low in fat (0.13%) and n the second group, 6 young dogs received the me diet except for the isocaloric substitution f 28% of the sucrose calories by fat in the form f fresh lard. All the animals in the first group howed the dry flaky skin which is characteristic f young dogs maintained on this fat deficient iet. The fatty acids of the serum were separated nto 3 fractions, namely, phospholipid, glyceride nd cholesterol ester fatty acids. The phosphoipid fatty acids were derived from the acetone nsoluble fraction of the serum lipids by saponiication and the glyceride and cholesterol ester atty acids were separated from the acetone soluble ortion by means of the castor bean lipase fracionation procedure. The amount of fatty acids as determined by microgravimetric means and he relative degree of unsaturation was measured y the iodine number of the fatty acids. The results show that the cholesterol ester fatty acids not only carry the most unsaturated fatty acids in the serum but also reflect to the greatest extent the character of the dietary regimen containing lard. Both the average amount and the degree of unsaturation of the glyceride fatty acids were the same in the 2 groups of dogs. The phospholipid fatty acids were slightly lower in amount and had lower iodine numbers in the group of animals on the low fat diet than those in the control group. The average iodine numbers in the two groups were 98 and 112 respectively. The average cholesterol ester fatty acid values were 111 mg. per 100 cc. serum for the group on the low fat diet and 138 mgm. per 100 cc. serum for the group receiving 28% lard. The average iodine numbers were 103 and 128 respectively. [*Aided by a grant from the National Live Stock and Meat Board through the National Research Council and Medical Graduate Research Fund of the Univ. of Minnesota.*]

Production of a scurvy-like condition of guinea pigs with glucoascorbic acid, and its prevention with ascorbic acid. D. W. Woolley. *Lab. of The Rockefeller Inst. for Medical research, New York.* It was demonstrated recently in this laboratory that mice and rats developed a disease with many of the manifestations of scurvy when they were fed glucoascorbic acid. This disease was not prevented by ascorbic acid, but was prevented by a substance present in plant materials rich in this vitamin. Since mice and rats do not require a dietary source of ascorbic acid, it seemed advisable to determine whether the scurvy-like disease could be prevented with the vitamin in a species such as the guinea pig for which ascorbic acid is a dietary essential.

The development of a satisfactory, highly-purified diet for guinea pigs (unpublished data) has made this test possible. Previous adequate diets for guinea pigs could not be used since they contained the protective substance mentioned above. With the present diet, composed of sucrose, casein, cellulose, salts, pure vitamins, and small amounts of a liver concentrate, the addition of 7 per cent of glucoascorbic acid to the ration, which provided 0.1 mg. of ascorbic acid per day, produced a disease within 10 days characterized by failure of growth, diarrhea, alopecia, mild hemorrhage, and death. Control animals which did not receive glucoascorbic acid did not exhibit these signs.

The disease was prevented by ascorbic acid. Thus, 1 mg. of ascorbic acid per day maintained health in guinea pigs receiving 5 per cent of glucoascorbic acid, and 10 mg. of ascorbic acid per day was effective in animals getting 7 per cent of the compound. Therefore, the disease may be viewed as an ascorbic acid deficiency, and the condition previously described in mice and rats may be regarded similarly.

THE AMERICAN ASSOCIATION OF IMMUNOLOGISTS

Abstracts of papers received from the Secretary of the Society. Since there will be no meeting in 1944 these papers are to be regarded as "read by title". For possible corrections in any of these abstracts see the next issue.

Occurrence of natural antibodies and formation of immune antibodies in rabbits of different ages injected with hemolytic streptococci. PAUL F. DEGARA. *Dept. of Pathology, Cornell Univ. Medical College, New York City.* Natural agglutinins for hemolytic streptococci were found in the sera of a number of untreated healthy young and full grown rabbits, but the titre was very low. No streptococcidal properties were noted in the sera of untreated young nor in those of full grown animals. Following a single intravenous injection of hemolytic streptococci, agglutinins developed in most of the young and of the full grown rabbits. In full grown animals a higher agglutinin titre was usually noted, and the agglutinins persisted for a longer period than in young rabbits. No streptococcidal activity developed in either young or full grown animals. The greater resistance of young rabbits to intravenous injections of hemolytic streptococci can not be explained by the presence of a large amount of natural antistreptococcal antibodies in the serum of the animals, nor is it due to a greater ability of the young rabbits to produce the antibodies following the intravenous infection.

Studies on the difference of resistance of young and of full grown rabbits to intravenous injections of hemolytic streptococci. PAUL F. DEGARA. *Dept. of Pathology, Cornell Univ. Medical College, New York City.* A single intravenous injection of broth culture of Streptococcus hemolyticus (strain NY5) was given to 29 full grown rabbits and to 32 young animals, 3 to 8 weeks after birth. Fourteen full grown rabbits (48.2 per cent) and 26 young rabbits (81.2 per cent) survived the injection for at least one week. Loss of the body weight was noted in all animals during the week following the infection. The body temperature of young rabbits rose sharply between 1 and 5 hours after the infection. It declined after 24 hours but remained above normal for 5 days. In full grown animals the initial rise was followed by a return of the body temperature to almost normal values after 24 to 30 hours. A second rise occurred 72 hours after the injection, and the temperature returned to normal after 6 days. Bacteremia was always present 5 hours after the injection of streptococci. After 24 hours the blood cultures from rabbits which survived the infection were either sterile or contained only small numbers of colonies, while those taken postmortem from rabbits that died within 7 days always contained innumerable streptococci. Arthritis was observed in the 26 young and in 12 of 14 full grown rabbits that survived the infection. The number of joints involved was greater in young animals. The greater resistance of young rabbits to streptococci may be explained by the fact that this age group did not yet have sufficient contact with the microorganisms and, therefore, was not "sensitized."

Studies on the effect of temperature, humidity, and glycol vapors on air-borne organisms.[1] K. B. DEOME and Personnel of USNR Lab. Research Unit #1. A dynamic system, consisting essentially of dust-free air moving through a long glass tube at a constant velocity enabled rapid estimations of air-borne bacterial death rates under controlled conditions of temperature and humidity. Glycol vapor was mixed with air in the tube. A test organism, *Salmonella pullorum*, was added and moved along with the air stream. Air samples taken from the tube at various distances from the dispersing atomizer contained organisms which had been exposed to the glycol vapors for known lengths of time. Increased death rates produced by the glycols were determined by comparison with normal death rates.

(a) Normal death rate: Changes in relative humidity (RH) between 40% and 60% produced little change in death rate; however, a lowered RH (15%) greatly increased survival time, while high RH (80%) produced the opposite effect. A rise in temperature from 28°C. to 37°C. progressively decreased survival time with every increase in humidity tested. Effects of combined increases in temperature and humidity were cumulative.

(b) Glycol death rate: Glycol effectiveness increased as concentrations approached the saturation capacity of the air, but decreased as temperature was raised from 28°C. to 37°C. and as the RH deviated from approximately 45%. The lo

[1] Dr. K. B. DeOme, Division of Veterinary Science, University of California, Berkeley, California. The Unit Personnel consists of: Albert P. Krueger, Captain MC-V(S), USNR, Officer-in-Charge, and A. H. Jacobs, Lieut. MC-V(S), USNR; A. [illegible] Browne, Lieut. H-V(S), USNR; O. J. Golub, Lieut. H-V(S), USNR; L. E. Rosenberg, Lieut. H-V(S), USNR; N. S. Wes[illegible] Lieut. H-V(S), USNR; J. R. Mathews, Lieut, H-V(S), USNR; M. D. Thaxter, Lt. (jg) HC-V(S), USNR; H. M. S. Watkin[illegible] Lt. (jh) H-V(S), USNR; A. J. Glazko, Ensign, H-V(S), USNR; W. R. Leif, Ensign, HC-V(S), USNR; G. B. Saviers, Ensign, HC-V(S), USNR; I. L. Shechmeister, Pharm. HC-V(S), USNR; A. I. Teplow, Pharm, HC-V(G), USNR; W. L. Axelrod, CPhM, V-6, USNR; H. R. Burkhead, PhM1c, V-6, USNR; E. R. Chisholm, PhM1c, V-6, USNR; C. R. Webb, Jr., PhM1c, V-6, USNR; W. D. Won, PhM1c, V-6, USNR.

survival time at 80% RH prevented demonstration of any reduction by glycol. High survival time at 15% RH was unaffected by glycol vapor even in high concentration. The concentration of PG required to produce a given reduction in death rate was more than one hundred times that of TEG. [*The opinions advanced in this paper are those of the writers and do not represent the official views of the Navy Department.*]

Neutralization of Middle East and Lansing strains of poliomyelitis virus by human sera. ISABEL M. MORGAN (by invitation), PETER K. OLITSKY and R. WALTER SCHLESINGER (by invitation). *The Rockefeller Institute for Medical Research, New York City.* A strain of poliomyelitis virus isolated from a fatal human case among the British Middle East Forces (MEF1), transferable to cotton rats and mice, was indistinguishable in its pathogenic and serological characteristics from Lansing virus (Science, **98**: 452, 1943). Human serum-neutralization tests were carried out with MEF1 and Lansing virus.

MEF1: Sera from the Middle East Forces included those from 15 British soldiers (2 poliomyelitis-convalescents and 13 "normal" men) and an American Medical officer. All these human sera neutralized MEF1 virus in intracerebral tests in mice.

Lansing virus: Sera from 3 Canadians (Winnipeg) and 27 male adult prisoners from New Jersey, as well as 12 British soldiers from the Middle East Forces convalescent from various diseases of the CNS were tested. All Winnipeg and New Jersey sera neutralized Lansing virus; 9 out of 12 Middle East sera were also positive.

Neutralizing antibody to Lansing type poliomyelitis virus was found in all "normal" sera from Canada, U. S. A., and the British Middle East Forces. Therefore, no diagnostic significance could be attached to the finding of similar antibody in convalescents of the Middle East Forces. [*This study was carried out under the auspices of the Neurotropic Virus Disease Commission, Board for the Investigation and Control of Influenza and Other Epidemic Diseases, Division of Preventive Medicine, Office of the Surgeon General, U. S. Army.*]

Laboratory and field studies of glycols and floor oiling in the control of air-borne bacteria. THE PERSONNEL[1] of United States Naval Reserve Laboratory Research Unit #1. *Univ. of California, Berkeley.* Laboratory experiments established that vaporized propylene glycol (PG) or triethylene glycol (TEG) raised the dew-point of air. The composition of glycol-water condensates resulting from glycol-air mixtures at various humidities is discussed in its relation to the theory of action of glycols on air-borne organisms. Methods of determining room air turnover, employing CO_2 or PG vapor as tracers, are described.

Field investigations conducted in a Navy hospital ward evaluated PG and TEG vapors, and the oil treatment of floors as to efficacy in reducing the total bacterial and hemolytic streptococcus counts of the air. Detailed observations were made on all ward routines to correlate various types of activity in the ward with the resultant data. It was found that such occurrences as sweeping, bed-making or the activity incident to morning routine and meal-time caused marked rises in both total and streptococcal counts. Neither PG nor TEG vapor in concentrations up to saturation produced significant reduction of bacterial levels under such peak conditions.

Swabbing floors with water, PG, PG-water mixtures, or with a light oil held down considerable dust, the major source of rises in counts; however, only oil was found to have the characteristics necessary to produce a lasting effect. One application of oil held all counts, except those following bed-making, to "quiet" levels for over a week and was partially effective after two weeks. The second application was completely effective for over two weeks.

Routine application of floor oils is recommended as a measure to reduce cross-infections. [*The opinions advanced in this paper are those of the writers and do not represent the official views of the Navy Department.*]

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[1] The Unit Personnel consists of: Albert P. Krueger, Captain, MC-V(S), USNR., Officer-in-Charge, and A. H. Jacobs, Lieut. MC-V(S), USNR; A. S. Browne, Lieut. H-V(S), USNR; O. J. Golub, Lieut. H-V(S), USNR; J. R. Mathews, Lieut. H-V(S), USNR; L. E. Rosenberg, Lieut. H-V(S), USNR; N. S. West, Lieut., H-V(S), USNR; M. D. Thaxter, Lt. (jg) HC-V(S), USNR; H. M. S. Watkins, Lt. (jg) H-V(S), USNR; W. R. Leif, Ensign, HC-V(S), USNR; A. J. Glazko, Ensign, HC V(S), USNR; G. B. Saviers, Ensign, HC-V(S), USNR; I. L. Sheshmeister, Pharm. HC-V(S), USNR; A. I. Teplow, Pharm. HC-V(S), USNR; W. L. Axelrod, CPhM, V-6, USNR; H. R. Burkhead, PhM1c, V-6, USNR; E. R. Chisholm, PhM1c, V-6, USNR; C. R. Webb, Jr., PhM1c, V-6, USNR; W. D. Won, PhM1c, V-6, USNR.

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CORRECTIONS OF ERRORS IN THE ABSTRACTS PUBLISHED IN THE MARCH ISSUE

Page 65. Georg Barkan. The sentence beginning on line 11 of the abstract should read: It is *now* analytically proven, with the oxidation product isolated and purified.

Page 79. Lawson and Thienes. On line 15, first column, the number 106 mg/K should be 1.06 mg/K.

Page 96. Susan Gower Smith. The parenthetical list of the eight synthetic vitamins reads (vitamins B_1 and B_2, riboflavin, etc.). It should read (vitamins B_1 and B_6, riboflavin etc.).

INTERIM REPORTS SUBMITTED BY THE SECRETARIES OF THE CONSTITUENT SOCIETIES

AMERICAN PHYSIOLOGICAL SOCIETY

The following interim actions of the Council are announced to the Society:

On May 4, 1943, the Council approved a new agreement with *Annual Reviews, Inc.* to replace the old one which was judged to be illegal.

On May 12, 1943, Dr. A. C. Ivy was appointed a member of the Board of Publication Trustees to fill the unexpired term of one year left vacant by the resignation of W. O. Fenn. On March 20, 1944, Dr. Ivy was appointed a member of the Board for the term 1943–1946.

The report of the Board of Publication Trustees (Dr. W. J. Meek, Chairman, Dr. A. C. Ivy, and Dr. H. C. Bazett) has been received and approved by the Council. The report announces the appointment of Dr. Hallowell Davis as Associate Editor of the Journal in place of Dr. Detlev Bronk, and of Dr. M. H. Seevers as Associate Editor of the Reviews in place of Dr. Geiling who retires. Both of these changes are made in accordance with the regular policy of rotation in office recommended by the Board. In 1943, the Board also appointed Dr. F. L. Hisaw an Associate Editor for Physiological Reviews in place of Dr. P. E. Smith who resigned.

Dr. Dayton J. Edwards was appointed alternate representative of the Society on the Council of the A.A.A.S. in May 1942. He and Dr. Homer Smith were continued as representative and alternate representative respectively in 1943. Representatives appointed for the Cleveland meeting in September 1944 are Dr. C. J. Wiggers and Dr. A. Sidney Harris (alternate).

The Council has approved the organization of two symposia for publication in Federation Proceedings. They are *Cerebral Blood Flow* by C. F. Schmidt and *Physiological Aspects of Convalescence and Rehabilitation* by Ancel Keys.

In 1943, the Council voted to recommend the following nominees to the Society for election as members: Harry F. Adler, Charles R. Allen, J. Garrott Allen, Clifford A. Angerer, William F. Bale, D. H. Barron, Edgar C. Black, Harry D. Bouman, John R. Brobeck, Katharine A. Brownell, Carl A. Bunde, George Clark, Julius H. Comroe, Jr., S. A. Corson, J. R. Di Palma, Victor A. Drill, C. H. Ettinger, William H. Forbes, Keith S. Grimson, R. E. Haist, J. E. Hawkins, Jr., A. W. Hetherington, S. M. Horvath, L. B. Jaques, Bruno Kisch, Max Kleiber, Harold Lamport, Julian P. Maes, R. A. McFarland, C. T. Morgan, C. A. Moyer, I. T. Nathanson, E. A. Pinson, Efren C. del Pozo, W. C. Randall, J. W. Remington, M. J. Schiffrin, G. M. Schoepfle, W. W. Scott, M. H. Soley, Clara Torda, D. B. Tyler, Shih-Chun Wang, D. F. Waugh, J. M. Werle, Grace E. Wertenberger, Herman S. Wigodsky, J. H. Wills, E. H. Wood.

All of these nominees are accorded provisionally all the privileges of membership until such time as the Society can complete the election in accordance with the Constitution.

The Council recommends that the dues for 1944 be set at $2.50.

Supplemental, May 15, 1944.

Dr. Homer Smith has been appointed to the Board of Publication Trustees for the 1944–47 term to succeed Dr. H. C. Bazett whose second term of office has been completed.

Dr. H. C. Bazett has been appointed to represent the Society on the Division of Medical Sciences of the National Research Council for three years to succeed Dr. Lawrence Irving.

The following members have been recommended by the Council for election by the Society at its next annual meeting: Marie Wecker Burrill, Leigh Edward Chadwick, William Doyne Collings, Alfred Lewin Copley, Andre Frederic Cournand,

B & Z Library

Jefferson Martineau Crismon, Robert Croly Darling, Edwin S. Fetcher, Dorothy Fetter, Piero Pio Foa, Leslie Willard Freeman, Austin F. Henschel, Theodore Louis Jahn, Robert Eugene Johnson, Jerzy Kaulbersz, Robert Cleveland Lee, Nathan Lifson, Victor Lorber, G. W. Manning, Gordon Marsh, Arthur W. Martin, Jr., Georges M. C. Masson, Augustus Taylor Miller, Jr., Evan William McChesney, Charles Neumann, Donald M. Pace, Charles Marc Pomerat, Hermann Rahn, David J. Sandweiss, Malvina Schweizer, Harry Shay, Irwin W. Sizer, J. Clifford Stickney, Henry Longstreet Taylor, Jay Tepperman, Julian M. Tobias, Richard Tyslowitz, Walter S. Wilde.

W. O. FENN
Secretary

THE AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, INCORPORATED

ABSTRACT OF THE EXECUTIVE PROCEEDINGS OF A MEETING OF THE COUNCIL, APRIL 28, 1943

OFFICERS AND COMMITTEES

Officers for the Year 1943–44: President, E. A. DOISY; Vice-President, A. B. HASTINGS; Secretary, A. K. BALLS; Treasurer, W. C. STADIE. Additional Members of the Council: R. J. ANDERSON, H. T. CLARKE, W. C. ROSE. Nominating Committee: D. D. VAN SLYKE (Chairman), G. O. BURR, H. B. LEWIS, W. M. CLARK, C. L. A. SCHMIDT, W. R. BLOOR, H. A. MATTILL, C. F. CORI, V. C. MYERS.

Editorial Committee (for the term 1939–45): P. A. SHAFFER (Chairman), A. N. RICHARDS, V. DU VIGNEAUD; (for the term 1941–47) W. R. BLOOR, H. A. MATTILL, C. L. A. SCHMIDT; (for the term 1943–49) H. D. DAKIN, J. M. LUCK, D. W. WILSON.

Editorial Board: To be chosen by the Editorial Committee.

Finance Committee: H. T. CLARKE (Chairman), R. J. ANDERSON, D. D. VAN SLYKE.

Assistant Treasurer: Irving Trust Company, New York City.

Counsel: LLOYD N. SCOTT, 535 Fifth Avenue, New York.

Representatives to the National Research Council: Division of Medical Sciences, A. B. HASTINGS (1942–45); Division of Biology and Agriculture, P. E. HOWE (1942–45).

Representatives on the Council of the American Association for the Advancement of Science: P. A. SHAFFER, V. DU VIGNEAUD.

Committee on Biochemical Nomenclature: E. M. NELSON (Chairman), H. C. SHERMAN, E. V. MCCOLLUM, E. S. G. BARRON.

Program Committee: The Council.

Representative on the Control Committee of the Federation Proceedings: C. G. KING.

Historian: R. H. CHITTENDEN.

Committee on Chemical Service to Medicine: V. DU VIGNEAUD (Chairman), D. D. VAN SLYKE, E. A. DOISY, ex. off.

Committee on National Defense: E. A. DOISY (Chairman), R. J. ANDERSON, A. K. BALLS, W. M. CLARK, H. T. CLARKE, A. B. HASTINGS, C. G. KING.

The Editorial Committee reported that during 1942, 560 manuscripts and 81 letters to the Editor were handled and a total of 4,273 pages was printed as compared to 5,100 pages in 1941. Publication of the Journal involved a net loss to the Society of $923.57. The format of the Journal has been changed to increase the number of words per page by about 18 percent.

The Treasurer reported that the running expenses of the Society for 1942 exceeded his receipts by $20.53. Cash on hand however was $1330.38. The Council authorized the Treasurer to purchase United States Bonds when he considered his balance justified doing so. The dues of the Society were retained at $2.50.

The Council authorized the preparation and printing of a Cumulative Index to volumes 126–150 of the Journal of Biological Chemistry, and its free distribution to subscribers. A limited number of copies of the previous Cumulative Indexes is still available and it was voted to supply such copies free to former subscribers of the Journal upon request until the number of each Index remaining is 75 copies. These remainders will be reserved for the Journal's use.

A history of the Society of Biological Chemistry has been written by Dr. Russell H. Chittenden. The Council authorized the Managing Editor of the Journal to publish this history as a separate item to be given to members free and to be offered for sale to other interested parties at a price to be determined by the Managing Editor. The Council also authorized payment of the usual expenses for running the Treasurer's and Secretary's offices and voted to appropriate from the treasury a sum of $1.00 per member to the Federation to pay for publication of the Proceedings.

The Council also authorized the President to appoint a Committee to make recommendations on revising the By-Laws.

The afternoon session was devoted to the Society's Committee on National Defense. The Council authorized the Committee to make a survey of the present activities of members and to take such steps as were found practicable to increase if possible participation in the war effort.

Deceased Members (as of April 28, 1943): Ross A. Gortner, September 30, 1942; Lawrence J. Henderson, February 10, 1942; Arthur D. Hirschfelder, October 11, 1942; Ondess L. Inman, July 21, 1942; Laurence S. Moyer, June 8, 1942; L. Pincussen, November 30, 1941.

ARNOLD KENT BALLS
Secretary

[The Council of the American Society of Biological Chemists held a meeting May 11 and 12, 1944. The Secretary's report of the business transacted was not available in time for publication in this (June) issue of the Federation Proceedings.—Ed.]

THE AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, INC.

ABSTRACT OF COUNCIL PROCEEDINGS, 1942–43

April 1942: The President appointed Drs. George B. Wallace and N. B. Dreyer, as representatives from The Society, to the Council of the American Association for the Advancement of Science and the Association of American Biological Societies.

July–October 1942: Because of war conditions and especially because of advice received by the Federation from Mr. Eastman, Director of Transportation, the question of holding the 1943 annual meeting was re-considered. In this connection, the Secretary wrote on two occasions to Mr. Eastman without receiving an answer. The Council voted 4 to 2 in favor of postponing the Cleveland meeting. Later the Federation Executive Council voted 10 to 2 for postponment.

August 1942: Dr. K. K. Chen, for the Eli Lilly Co., offered The Society a $1000.00 prize, yearly, for a period of three years. This prize, to be called "*The John J. Abel Prize*" is to be given to the member of The Society presenting "the most meritorious pharmacological research" at the Annual Meeting. With the prize, is to be given a gold medal, inscribed, "given by the Eli Lilly Company."

This generous offer was accepted by the Council.

During the next few months the Council studied methods of awarding the prize but was unable to arrive at a satisfactory solution. It was therefore decided that the method of awarding this prize be decided by the members at the next Annual Meeting.

January 1943: In lieu of an Annual Meeting abstracts were collected and published in the Federation Proceedings.

April 1943: The Council voted to approve the request of the Treasurer, Dr. Nelson, to close the books.

The books were audited by Drs. Chapman Reynolds and Gerhard Katz.

Deceased Members: Brown, Wade Hampton, Aug. 4, 1942; Cohen, Seymour J., June 11, 1942; Crile, George W., Jan. 7, 1943; Hirschfelder, Arthur D., Oct. 11, 1942; Walton, D. C., Mar. 6, 1942.

RAYMOND N. BIETER
Secretary

ABSTRACT OF COUNCIL PROCEEDINGS, 1943–44

The officers and committees elected at the Boston Meeting in 1942 were continued over into this year, in the absence of an Annual Meeting.

May 1943: Dr. Carl Schmidt asked to be relieved of his position of Editor in Chief of The Journal of Pharmacology and Experimental Therapeutics. His resignation was accepted by the Council.

Dr. George B. Wallace was elected to the position of Editor in Chief of The Journal by the Council, on a year to year basis. Dr. Wallace accepted the position.

August 1943: The Treasurer, Dr. Nelson, recommended that the dues for 1943–44 be $2.00. The Council voted to approve this recommendation.

September 1943: The Federation Executive Committee voted not to hold an annual meeting in 1944 by a vote of 9 to 2.

October 1943: The Treasurer, Dr. Nelson, was instructed to send Dr. Hooker, Federation Secretary-Treasurer, a check for $283. ($1 per member) for the Federation Proceedings.

December 1943: Professor F. R. Winton, Acting Secretary of the British Pharmacological Society, wrote that Professor J. A. Gunn wished to retire as their representative on the Editorial Board of The Journal of Pharmacology and Experimental Therapeutics, and it was suggested that Professor J. H. Gaddum succeed him.

The Council voted to accept the resignation of Professor Gunn and to approve the appointment of Professor Gaddum. The Council furthermore voted to instruct the President to send a letter of

appreciation to Professor Gunn for his long and valuable service on the Editorial Board of The Journal.

The vote of the Council to hold the Annual Meeting in Cleveland in 1945 was a tie, three for and three against. The Federation Executive Council voted 10 to 3 in favor of holding this meeting.

The Council voted not to arrange a Symposium in manuscript form for 1944.

The Council voted to arrange a by-mail election of officers and new members in the spring of 1944.

January 1944: In lieu of an annual meeting, abstracts were collected and published in the Federation Proceedings.

January–March 1944: The Council voted to hold a Council Meeting in Baltimore, to notify the members of this meeting and to request proposals for membership, and to invite the Membership Committee and the Chairman of the Nominating Committee. The date of the meeting was set for April 19–20 at Hotel Stafford. Notices concerning these activities were sent to the members on January 1, and March 22, 1944.

March 1944: The National Research Council notified the Secretary that the term of Dr. E. K. Marshall, Jr., The Society's representative to the Division of Medical Sciences expires June 30, 1944. The name of the new representative was requested by April 1st. The Council voted to elect Dr. E. M. K. Geiling as The Society's representative, and so notified the National Research Council.

ABSTRACT OF COUNCIL MEETING, APRIL 19–20, 1944

The meeting was called to order by the President in the Hotel Stafford, Baltimore, Md. at 9:30 A.M. Those present were: E. K. Marshall, Jr., President; C. A. Dragstedt, Vice-President; E. E. Nelson, Treasurer; McKeen Cattell, Councilor; Ralph G. Smith, Councilor; Harry Gold, Chairman, Membership Committee; M. H. Seevers, Membership Committee; H. B. Haag, Membership Committee; H. O. Calvery, Chairman, Nominating Committee; Raymond N. Bieter, Secretary.

The reading of the Minutes was dispensed with since they were approved by last year's Council.

The Secretary read the abstracts of the Council Proceedings for 1942–43 and 1943–44. These were approved for publication in the Federation Proceedings together with this abstract of the Council Meeting.

Reports received, read and accepted. In each instance it was also voted to instruct the Secretary to file the complete reports.

1. Report of Dr. N. B. Dreyer, Society Representative, on the meeting of the Union of American Biological Societies in February 1943 in Philadelphia.

2. Report of Journal Editors: that of Dr. Carl F. Schmidt covered the period, March 28, 1942 to June 30, 1943, and that of Dr. George B. Wallace covered the period, July 1, 1943 to April 1, 1944.

3. Report of the Treasurer, Dr. E. E. Nelson. The President appointed Drs. M. H. Seevers and Herbert O. Calvery auditors. The auditors approved the report.

Dr. Nelson moved that the dues for the coming year be $3.00. This was approved.

Dr. Nelson moved it be recommended to The Society that The Society pay, at least in part, the expenses of the Treasurer to the Annual Meeting because the Treasurer holds office for a number of years, thus necessitating his presence at every meeting whether he can afford it or not. This was approved.

4. Report of the Nominating Committee, submitted by the Chairman, Dr. Herbert O. Calvery. The Council approved a ballot to be submitted to the members by mail.

5. Report of the Membership Committee, submitted by Dr. Harry Gold, Chairman, and Drs. M. I. Seevers and Harvey Haag. As a result of the joint meeting of the Membership Committee and the Council, a list of 33 names will be submitted to the members of The Society. This ballot, to be submitted by mail, was approved by the Council.

On September 20, 1943, Dr. Chauncey D. Leake wrote to the Secretary requesting that the Council consider the question of union of The Society for Experimental Biology and Medicine and The Federation. After considerable discussion the Council voted not to recommend this to The Federation Executive Committee because of the differences in character and purpose of the two societies.

On February 17, 1944, Drs. Robert A. Woodbury and Benedict E. Abreu wrote to the Secretary requesting that the Council consider the question of encouraging Edwards Brothers, Ann Arbor, Michigan, to prepare a preprint of Heffter's Handbuch der Experimentellen Pharmakologie under the jurisdiction of the Alien Property Custodian. The Council voted to approve this recommendation and to call the attention of all members to this action.

Deceased Members: Barbour, Henry Gray, Sept. 23, 1943; Bullowa, J. G. M., Nov. 9, 1943; Coombs, Helen C., Mar. 4, 1944; Ets, Harold N., June 25, 1943; Hatcher, Robert A., April 1, 1944; Henderson, Yandell, Feb. 18, 1944; Koller, Carl, Mar. 21, 1944; Salant, William, Dec. 10, 1943; Wallace, Edward W., July 11, 1943.

RAYMOND N. BIETER
Secretary

THE AMERICAN SOCIETY FOR EXPERIMENTAL PATHOLOGY

INTERIM REPORT OF THE SECRETARY

(March 31, 1944)

Officers and Committees

President: Balduin Lucké, University of Pennsylvania, Philadelphia, Pennsylvania.

Vice President: Paul R. Cannon, University of Chicago, Chicago, Illinois.

Secretary-Treasurer: H. P. Smith, State University of Iowa, Iowa City, Iowa.

Councilors: Douglas H. Sprunt, Duke University, Durham, N. C.; Frieda S. Robscheit-Robbins, University of Rochester, Rochester, N. Y.

Representatives on the Council of the American Association for the Advancement of Science: Malcolm H. Soule, University of Michigan; E. B. Krumbhaar, University of Pennsylvania.

Representative on the Council of the Union of American Biological Societies: Morton McCutcheon, University of Pennsylvania.

Representative on the Eli Lilly Award Committee (Jointly with Society of American Bacteriologists): For Nominations: Doctor Morton McCutcheon, University of Pennsylvania; For Award: Doctor Shields Warren, Harvard University.

The last regular meeting of this Society was held in Boston, April 1–3, 1942. The meetings scheduled for the Spring of 1943 and for the Spring of 1944 were cancelled because of the war and the attendant difficulties in securing transportation and hotel accommodations. In order to carry on the reduced functions of the Society, the following question was sent to all members of the Society: "Shall the present members of the Council be authorized to hold office for the period of the emergency?" The vote was 209 to 5 in favor of the proposal.

The Council then considered the advisability of holding a series of small regional meetings in order to provide an opportunity for discussion of current papers and problems. It was recognized, however, that a very large percentage of our members are directly concerned in the war effort and that regional meetings would probably not be very successful. It was decided, therefore, to defer action on this proposal.

In accord with the policy of the Federation, members of this Society contributed short abstracts of current work for publication during 1943 and 1944 in the Federation Proceedings.

No additional members have been elected to the Society since the last regular business meeting. Several nominations have been received. Consideration is being given these cases by the Council.

The total membership as of March 21, 1944 was 296. Resignations of Doctors John F. Anderson, Stuart Graves and J. E. Sweet have been received and accepted by the Council. The Council notes with regret the death of the following members: Dr. Wade H. Brown, August 4, 1942; Dr. Andrew Watson Sellards, December 1, 1942; Dr. H. Gideon Wells, April 26, 1943; Dr. Carl Wesley Apfelbach, June 25, 1943; Dr. Karl Landsteiner, June 26, 1943; Dr. Leslie T. Webster, July 12, 1943.

The records of the Treasurer show receipts of $850.48 and disbursements of $788.93 during the period of this report. Total cash on hand, March 31, 1944 was $1478.12.

H. P. Smith, M.D.
Secretary-Treasurer

AMERICAN INSTITUTE OF NUTRITION

RÉSUMÉ OF THE COUNCIL MEETING, MARCH 27, 1944

In the absence of a regular meeting of the Institute, the Council met in special session in Detroit on March 27, 1944.

Note was taken of the death of two members of the Institute during the past year, namely, Dr. Russell H. Chittenden and Dr. L. S. Palmer.

After extended discussion, the Council decided that due action should be instituted regarding changes in the By-Laws with respect to the limitation of the number of members and also as regards Emeritus membership.

The following were approved for election to membership: R. H. Barnes, J. P. Chandler, G. K. Davis, A. H. Free, Jean E. Hawks, D. M. Hegstedt, Gladys M. Kinsman, J. K. Loosli, L. W. McElroy, W. A. Perlzweig, Thelma Porter, V. P. Sydenstricker, M. W. Taylor, A. DeM. Welch.

The Editor of the Journal reported that: During the year 1943 volumes 25 and 26 of the Journal of Nutrition were published; they contained 121 papers. There were submitted for publication during the year 176 articles. The average number of papers printed per issue in volumes 25 and 26 (including in the calculation the pages needed for the index) was 10.9, which represented a slight

improvement over the preceding year and approximated very well the 10 which the editorial policy strives for.

During the year a combination of circumstances operated to cause a delay in appearance of various issues. The Federal Government has established a system of censorship of scientific publications. Loss of key trained personnel from the printing shop was another contributing factor; this made it necessary for Wistar Institute to undertake to train many new people. As a result of the various efforts made, the delay in appearance of issues has been steadily decreasing. If no further complications arise, it is reasonable to expect that some time during 1944 issues will begin to appear in accordance with the usual schedule.

On January 15, 1944, the War Production Board issued its paper limitation order restricting the allowance of paper to 85 per cent of that used in 1943. Because of this it became necessary to increase the amount of printed material per page. This was easily accomplished by reducing the size of the margins. The binding size of the Journal was not changed. The February, 1944, issue was the first to be printed with this new format.

The five-year term of the Editor expired during the spring of 1944. The Editorial Board therefore conducted an election and re-elected the Editor for another term.

The Council expressed appreciation of the satisfactory way in which the Journal had been managed by the Editor and Associate Editors.

The Secretary reported that the appropriate committee of Judges had selected Dr. A. G. Hogan as recipient for the Mead, Johnson & Co. Vitamin B Complex Award and Dr. E. V. McCollum for the Borden Award. In this connection, the decision was reached that henceforth the anonymity of Committees of Judges of all awards given under the auspices of the American Institute of Nutrition be permanently preserved.

The Treasurer's report, audited by Drs. F. S. Daft and G. J. Cox, was presented. As of March 1, 1944, there was a cash balance of $803.04 which sum includes a balance of $87.14 from funds deposited with the Institute by Nutrition Abstracts and Reviews for expenses incident to the work of the American Editor. There was an overall gain of $73.40 in the past year.

The dues for 1944–45 were fixed at $2.00 per member and it was recommended that $1.00 per member be paid from the Treasury for support of Federation Proceedings. The Council voted $25.00 for the past year secretarial assistance for the Treasurer and $25.00 each for the Secretary and Treasurer for the same purpose for the coming year. The Council acted to approve a grant of $10.00 from the Treasury in support of the Placement Service of the Federation.

President Lewis appointed the following Nominating Committee for 1944–45: Drs. H. A. Mattill, Chairman, N. B. Guerrant, A. C. Hogan, F. J. Stare and Jet C. Winters.

Dr. L. A. Maynard was reappointed as representative of the Institute of Nutrition to the Division of Biology and Agriculture of the National Research Council.

Action on the invitation to join the Union of American Biological Societies was deferred by the Council until the subject could be discussed in open meeting.

Arthur H. Smith
Secretary

SYMPOSIUM ON SUBSTITUTES FOR ANIMAL PROTEIN IN NUTRITION

INTRODUCTION AND DISCUSSION OF THE AMINO ACID COMPOSITION OF PLANT SEEDS

HUBERT BRADFORD VICKERY, Chairman

Connecticut Agricultural Experiment Station, New Haven, Conn.

The use of plant seeds as food is one of the most ancient as well as one of the most universal practices of mankind. Although innumerable kinds of seeds find their way into the human diet, the most extensive use is made of two great classes of plants, the cereal grains of the grass family on the one hand and the legumes on the other. Wheat, rye, barley, oats, corn and rice make up the greater part of the commonly used seeds of the one class; and the balance of the vegetable protein that is consumed is furnished by the beans, peas, lentils and especially in the Orient but increasingly in America by the soy beans. Together, these kinds of seeds form the basis of the diets of the greater part of humanity.

Under the conditions of relative plenty that exist in the United States, it is rare that reliance is placed for any protracted length of time upon a diet that consists of a single kind of seed. Experience and instinct alike dictate that more or less

variety be introduced. Deficiencies in one or another dietary essential are therefore in general compensated, and pronounced symptoms of deficiency diseases are seldom encountered. At the present time, however, there are restrictions upon the free choice of dietary components and, for economic as well as strategic reasons, substitutions among foodstuffs have become essential.

It is the purpose of the present symposium to consider certain aspects of the dietary problems that are thus raised, and to show, in so far as this is possible, that substitution if wisely made in itself involves no necessary dietary risk despite the violence it may do to personal tastes and habits.

It is traditional in this country to include in the diet a large proportion of proteins of animal origin. According to estimates recently made (1), meat, dairy products, eggs and poultry have together furnished from 52 to 57 per cent of the average protein intake, the grains from 28 to 37 per cent, and fish between 2 and 3 per cent. This distribution is the result of a complex of economic conditions and food habits; in the present war emergency some modification is inevitable.

Because of the prospective shortage in the production of animal proteins and of the increased demands upon American sources of these proteins by our allies, this modification must take the direction of an increase in the proportion of proteins of vegetable origin used in the average diet. Surveys of the situation made under the auspices of the Food and Nutrition Board of the National Research Council have indicated that only a limited number of vegetable foodstuffs need be considered in any large scale program of substitution. Soy beans, peanuts, wheat germs, corn germs, and the so-called food yeasts are the chief products that are being, or can be, made available in the large quantities that are necessarily involved, and attention is therefore restricted in this symposium to the proteins of these materials.

Experience with a number of purified proteins from animal sources has shown them to contain all of the amino acid components that are required for growth, for maintenance in health, and for reproduction, if fed to animals at certain levels of intake in otherwise adequate diets. An estimate of the adequacy of some other protein, or protein-rich foodstuff, may therefore be made in terms of one or other of the better-known proteins employed as a standard. Casein or lactalbumin has frequently been used for this purpose where emphasis has been placed upon freedom from non-protein components in the standard material. Otherwise such materials as whole egg-white protein, or meat protein have been employed.

For this type of comparison, isolation of the pure proteins from the material under examination is not essential. In the case of a plant seed, it suffices to compare the nutritive effect of the whole seed meal or protein concentrate therefrom with the arbitrarily chosen standard in properly designed feeding experiments. The results of numerous tests of this type upon the nutritive effect of soy beans and of peanuts are described in the paper by Jones, together with tests of the supplementary effect of these materials upon the proteins of wheat. Analogous experiments upon the nutritive effects of the germs of wheat and of corn are reviewed by Stare and Hegsted.

Although large amounts of yeast are produced and used for animal feeds in this country, the quantities that find their way into human food are not great. Nevertheless, yeast, and especially the newly developed varieties of *Torula* yeasts appear to offer important possibilities as food for man. The present situation with respect to the use of yeast as human food is reviewed in the paper of Carter and Phillips. In the final paper McCay discusses, from the point of view of one concerned with the feeding of men in the armed forces, the general problem of the enrichment of bread and other bakers' products with protein of superior nutritive value.

Direct comparison of one foodstuff with another is not, however, the only way in which an estimate of values in nutrition can be made. If accurate information on the amino acid composition of a vegetable foodstuff can be secured, it becomes possible to make an estimate of its absolute value as a source of food protein. Some of the factors involved in the solution of this difficult problem are discussed in the following paper.

ON THE AMINO ACID COMPOSITION OF PLANT SEEDS

The adequacy or inadequacy of a given protein to promote the growth of young animals or to maintain fully grown animals in nitrogen equilibrium has been shown to depend on the composition of the protein with respect to the amino acids that it yields. Even if only one of the ten amino acids known to be essential (2) is supplied in less than optimal quantities, nutritive failure results. Accordingly the problem of the substitution of one protein for another in the diet can be reduced to the question of the relative composition with respect to these amino acids. If this composition is known, one can predict with some assurance the levels at which the two proteins will give essentially the same nutritive effect. Furthermore, in those cases where there is a marked deficiency in one or more amino acids, it becomes possible to select supplementary proteins rich in the particular amino acids and to correct the deficiencies. Knowledge of the amino acid composition both of the standard proteins or protein foodstuffs and of the products to be considered as partial or complete substitutes for them is therefore essential to

an intelligent selection of the components of a mixed protein diet.[1]

It is the purpose of the present discussion to point out some of the difficulties that arise when complete and accurate information is required upon the amino acid composition of the vegetable products that are being advocated as partial substitutes for the better known proteins of animal origin in the human diet. These difficulties are of two kinds; the purely technical ones that arise from the inadequacies in analytical methods, and the far more serious ones that have to do with the selection, preparation and purification of the protein material that is to be subjected to analysis.

The situation with respect to analytical methods for the determination of the amino acids essential in nutrition has been enormously improved within the past three years. A survey made a few years ago (7) suggested that of the ten amino acids concerned, only five (tryptophane, methionine, arginine, histidine, and lysine) could be conveniently determined with a satisfactory degree of accuracy. As a result of recent increase in interest in amino acid chemistry as well as in nutrition, it is probable that today data upon all ten essential amino acids can be readily secured with an accuracy adequate for most practical purposes and with only a moderate expenditure of time and material.

The vital problem of the determination of threonine has been solved by the publication of the beautiful method of Shinn and Nicolet (8) which has now been widely applied to proteins important in nutrition (9).

The baffling question of the separate determination of valine, leucine, and isoleucine seems now on the point of being finally answered. These three mono-amino acids have long presented almost insuperable difficulties. The data secured by the early investigators, who of necessity employed the Fischer ester distillation method, provided sound qualitative information with respect to valine and to the mixture of the two leucines, but there could be no assurance of the quantitative accuracy. However, minimal levels were established for a number of important proteins and these served many practical requirements pending the development of more accurate methods. The publication, during the past year, of a series of papers (10, 11, 12, 13, 14) in which microbiological methods for the separate determination of valine, leucine, and isoleucine are described has placed the analytical chemistry of these substances upon an entirely new footing. Although the solubility product method of Bergmann and his associates (15), as well as the isotope dilution method of Rittenberg and Foster (16, 17), have been employed for the determination of leucine, neither method has as yet been widely applied. Accordingly, although data by these highly accurate methods are greatly to be desired to establish the leucine content of at least a few important proteins in order to provide controls upon the accuracy of other procedures for the determination of leucine, the new microbiological methods are particularly welcome inasmuch as they render it possible to determine all three amino acids independently. All of the difficulties of these methods do not yet seem to have been surmounted since the agreement among the different workers in the field still leaves something to be desired. Nevertheless there is little doubt that, within a relatively short time, information on the composition of many proteins with respect to these substances will have become available.

The determination of phenylalanine still remains somewhat of a problem. A colorimetric method was described some years ago by Kapeller-Adler (18) which has been extensively used by Block both in its original form and in a modification (19), but neither the solubility product method nor the isotope dilution method has yet been adapted to this purpose, and thus the necessary data to serve as evidence of the accuracy of the much more convenient colorimetric method are still lacking.[2] On the other hand, Gordon, Martin and Synge (20) have recently described a method of partition chromatography for the separation of

[1] It should be emphasized that these statements are based upon growth and nitrogen equilibrium studies conducted with animals. With respect to the situation in human nutrition, Rose (3, 4) has recently shown, 1) that the twelve amino acids previously demonstrated to be dispensable for rats and dogs in growth experiments are likewise dispensable for the maintenance of nitrogen equilibrium in man for a period of 8 days; 2) that a mixture of the ten amino acids previously shown to be indispensable for the growth of rats adequately maintains nitrogen equilibrium in man for 8 days; 3) that valine, methionine, threonine, leucine, isoleucine and phenylalanine are necessary constituents of the diet of man; and 4) that histidine is not necessary for the maintenance of nitrogen equilibrium in human subjects at least for a short period of time. Holt and his associates (5) have presented evidence that tryptophane and lysine are necessary to maintain nitrogen equilibrium in man and that a temporary deficiency of arginine, although it does not result in a negative nitrogen balance, gives rise to a reduction in the number of spermatozoa. More recently (6) they have reported that methionine is also essential for the preservation of nitrogen equilibrium in man but that trials with cystine led to inconclusive results.

[2] There is little doubt that a microbiological method will shortly be developed. An attempt to do this has already been made by Hegsted (13).

the mono-amino acid components of protein hydrolysates which appears to hold considerable promise, especially for the determination of phenylalanine. Again, however, too few data by this new method have yet been accumulated to serve as a control on other procedures.

It would appear, from what has been said, that the accurate determination of the amino acids of greatest significance in nutrition is today a problem to which a moderately satisfactory answer can be given. The situation is quite different with the application of the analytical methods to the vegetable products now becoming of greatest significance as substitutes for animal proteins in the human diet.

What is needed is a statement of the amino acid composition of the *total* protein of these vegetable products. What is to be found in the literature are more or less incomplete and seldom entirely trustworthy tables of the composition of purified samples of the chief protein components. What is usually entirely lacking is accurate information upon the ratio of the quantity of the protein components that have been analyzed either to the total protein or to the weight of the seed itself. Furthermore there is practically no information whatever available regarding the composition or the relative quantity present of the subsidiary or minor proteins of these foodstuffs.

The opinion appears to be widely held that all that is required is to subject samples of the foodstuff directly to hydrolysis for the liberation of the amino acids and to carry out the specific analytical procedures upon the solution that is thereby secured. Purification of the material by extraction with fat solvents would doubtless be generally recognized to be desirable, but separation of the proteins themselves from the other components as a prerequisite to analysis is not at all universally considered to be essential.

The issue is really one of the degree of accuracy that is needed for practical application of the results of amino acid analysis to the problems of nutrition. If all that is wanted is a demonstration that the proportion of one or more of the essential amino acids present is greater than a certain minimal proportion related to the level at which this amino acid must be fed in order that it shall not become the limiting factor in growth, then it is true that analysis of the impure protein concentrate or of the fat-free meal might provide adequate information. However, in the event that the particular amino acid were present normally at so low a level that the losses that are experienced during hydrolysis of the crude protein preparation remove a significant part of it, the information obtained might well lead to a misapprehension of the nutritive value of the material under consideration.

Most vegetable products employed as foodstuffs contain, in addition to protein, a large proportion of starch, cellulose, complicated compounds that yield uronic acids on hydrolysis, and a wide variety of allied substances that may be summed up under the general term carbohydrates. When proteins are subjected to acid hydrolysis in the presence of carbohydrates, a considerable proportion of the nitrogen of the protein is found in the hydrolysate in the form of a black insoluble product known as humin. It has long been known that the whole of the nitrogen originally present as tryptophane is found in the humin fraction even when highly purified samples of protein are hydrolyzed with acid, but the origin of the larger proportions of humin nitrogen that are obtained when impure samples of protein are hydrolyzed is still unknown. The presence of sulfur in such humin (21) leads to the inference that cystine and methionine are in part destroyed, but which of the other amino acids also contribute and to what extent is still for the most part a matter of speculation. Some information on the point is given in recent experiments of Kuiken and his associates (10) who have demonstrated small but significant losses of valine, leucine, and isoleucine when casein is hydrolyzed in the presence of carbohydrates. One may therefore infer that these essential amino acids can under such conditions also contribute to the formation of humin. Thus more or less grave losses of at least five of the ten essential amino acids are known to be a possibility when impure specimens of protein are subjected to acid hydrolysis, and it is obvious that the accurate analysis of so crude a mixture as a seed meal offers difficulties that hitherto have not been surmounted.

The isolation of the protein components in a state of purity and the analysis of these is an alternative solution of the problem. This was the approach in the classical work of Osborne and Mendel and, in spite of the amazing development of the field of nutrition since that time, little in the way of improvement over their fundamental principle has been suggested. It is especially unfortunate, therefore, that research upon the isolation and purification of vegetable proteins has not kept pace with the progress in the techniques of amino acid analysis nor with the advances in many other branches of protein chemistry. At the risk of placing tedious emphasis upon facts so elementary as to be obvious, it may therefore be permissible to discuss briefly the problems presented by the isolation of the protein components of plant seeds in such a degree of purity that analyses of real value to the student of nutrition may be secured.

Plant seeds in general contain one or two, or sometimes several main proteins that represent

the reserve material upon which the young plant relies for its supply of nitrogenous nutriment during the earliest stage of growth. In the cereal grains, this protein is laid down in solid form in the cells of the endosperm where it is usually accompanied by more or less starch which is likewise stored as a source of nutriment. In the legumes, the protein is found often in definite granules in the cells of the two cotyledons together with some starch, but usually an appreciable proportion of fat is present in addition. The storage proteins of seeds are characterized by a considerable degree of chemical stability and they are not usually supposed to share in the vital processes of the cells in the way that the protoplasmic and enzyme proteins of living cells do.

Seeds also contain a small structure known as the embryo which develops, when the seed is supplied with moisture and oxygen at the correct temperature, into a hypocotyl which carries at its upper end the first embryonic leaf or leaves, and the lower portions of which become differentiated into stem and root tissue. The seed is thus a complex structure anatomically and contains many different kinds of cells each of which has its own functions and, accordingly, each of which has its own characteristic chemical composition.

Obviously many different kinds of protein must be present besides the main or storage proteins that are usually thought of when seed proteins are mentioned. It is futile, in the present state of our knowledge, to attempt to list the several kinds. However, the endosperm or cotyledon tissue must contain, in addition to the storage proteins, the proteolytic enzymes, themselves proteins, which render the storage proteins soluble at the time of sprouting, together with the enzymes required to convert the starch, fat, and other components into water-soluble substances that can be translocated into the tissue of the growing embryo and there reorganized into new components or otherwise utilized. The embryo tissue, in turn, must contain the equipment of enzymes[3] necessary for the usual functions of the living cell; those required for respiration, for specific synthetic processes and so forth, together with the proteins of the protoplasm. Clearly, therefore, the mixture of individual proteins that is obtained when plant seeds are ground and extracted with suitable solvents must be far from simple.

The classical approach to the problem of the isolation of the proteins of seeds is, first, to devise conditions with respect to the temperature, ionic strength, hydrogen-ion activity and nature of the solvent under which as much as possible of the nitrogen of the seed meal can be brought into solution. After clarification of the solution, the physical conditions are then so modified that as much as possible of the protein separates as a solid phase. Subsequently fractionation of the product is attempted, again by suitable modification of the physical conditions of the solution, and chemical analysis of the fractions obtained is relied upon to characterize them. Where differences in physical or chemical properties of the fractions can be established, the conclusion is drawn that different individual substances have been more or less completely separated from each other. Where the successive fractions do not differ significantly in properties, the tentative conclusion is drawn that they represent the same substance. If, by repetition of the preparation with as many modifications of the method as conditions allow, a product of the same physical and chemical properties is invariably secured, there is some justification in concluding that a specific and characteristic protein component of the seed has been obtained.

As a rule, an investigation of this type results in the isolation of one or more fairly well characterized preparations that represent the larger part of the total protein of the seed as indicated by nitrogen analysis, together with minor quantities of less clearly defined material. It is commonly assumed that the protein or proteins present in dominant proportion represent the reserve or storage protein of the seeds. However, save in the early work of Osborne, little attention has usually been given to the fractions that are obtained in only small yield. It is clear, from the considerations discussed above, that preparations of the proteins present in minor proportion can scarcely be expected to represent homogeneous material unless special techniques are employed, as for example in Sumner's isolation of crystalline urease from jack bean meal (23). The interest has usually been in the protein or proteins present in large proportion, and it is this part alone that has ordinarily been studied with respect to amino acid content, physical properties and nutritive effect. Furthermore, because of the special interest in accuracy of characterization, emphasis has customarily been placed upon purification at the expense of yield.

As a result, only a few of the studies of seed proteins that have followed the classical pattern, including even those of Osborne himself, contain satisfactory information on the relative proportions of the main protein components that are present, and still less information is available regarding either the composition or the relative proportions of the less well characterized minor components. Nevertheless it may frequently be true that the composition of the minor proteins is

[3] Horvath (22) lists amylases, diastases, proteases, lipases, urease, uricase, oxidases, and peroxidases as having been detected in soy beans and gives references to the literature.

such that they serve to supplement the nutritive effect of the main protein with respect to one or more amino acids in which this protein is deficient. Examples of exactly this type of supplementary effect are known, the details of the case of arachin and conarachin, the main and one of the minor proteins of the peanut, being given in the following paper by Jones.

Quantitative isolation of the main proteins in a state of purity, as well as of the fractions that represent the subsidiary proteins, is indeed the ideal towards which research in this field should strive, but it is not an indispensable step in the process of obtaining information on the true amino acid composition of vegetable foodstuffs. For many practical purposes it would suffice if preparations that represent accurately the *whole protein* of the product could be secured, provided that these preparations can be rendered so free from non-protein contaminants that the humin formed during acid hydrolysis includes only a truly negligible proportion of the nitrogen. This problem has not, as yet, been adequately solved although there are techniques known today that would appear to render it a promising line of attack. A praiseworthy effort to accomplish this has indeed been made by Block and Bolling (24, 25) for several of the materials of interest at the present time as substitutes for the more widely esteemed animal proteins, and an indication of the present state of knowledge of these materials is given in the following papers.

Emphasis is placed upon the importance of this approach since our present information is unfortunately limited in its scope. It has long been conventional to apply newly developed analytical methods for amino acids to such well-known animal proteins as casein, egg albumin, hemoglobin, fibrin, or gelatin, and to an occasional vegetable protein such as edestin, wheat gliadin, and zein. Up to a year or so ago, amino acid analyses of preparations of such proteins as wheat or corn glutenin, soy bean or peanut globulins, or of the isolated proteins of wheat or corn germs would have been regarded as being chiefly of academic interest. Today this information is urgently needed. Although much can be learned by comparative studies of the nutritive effects of whole seed meals or of the flours and concentrates prepared from them, the knowledge so obtained with respect to relative supplementary food value remains and will remain empirical until accurate information concerning the amino acid composition of the proteins they contain has been secured.

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NUTRITIVE VALUE OF SOYBEAN AND PEANUT PROTEINS

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Soybean proteins. For centuries the soybean has been the chief source of protein in the diet of millions of people in the Orient. It is only comparatively recently that its value as a source of high quality protein has been recognized in the Occident. In the United States it was not until the first World War that any general interest was manifested in the soybean as a possible source of high quality protein. Until very recently the small amount produced was valued chiefly as a source of oil, and the by-product, the press cake, was used as a feedstuff for farm animals. In a land of plenty, where there is an abundance of meat, milk, and eggs for all, it is natural that little thought was given to other sources of high quality protein, especially for human consumption.

The classical work of Osborne and associates on the proteins of the soybean and their nutritive value (1, 2, 3, 4, 5, 6) stimulated an increasing amount of investigation on the nutritional properties of soybean proteins. There is today an extensive literature bearing almost unanimous testimony that the proteins of properly processed soybeans have a high nutritive value.

Anticipating a reduced supply of animal proteins in the United States during the war emergency, the Food and Nutrition Board of the National Research Council in 1943 passed a resolution recommending the use for human food of vegetable proteins of superior biological value, among which soybeans and peanuts were emphasized. Large quantities of soybean flour and soybean grits are being used by the Army and shipped abroad for Lend-Lease supplies. Increasing amounts of soybean products are also being used in this country for civilian consumption.

The soybean is one of the richest known sources of protein among naturally occurring foods, ranging, according to variety, from 30 to 45 per cent.

The superior nutritive value of cooked soybean protein has been demonstrated by numerous investigators by laboratory feeding experiments with rats (1, 7, 8, 9, 10, 11, 12, 13). Tests conducted at agricultural experiment stations, as well as the extensive use of soybean meal in the practical feeding of farm animals, have shown that, in general, soybean proteins have a high nutritive value. There is evidence, however, that not all animals can utilize soybean protein with the same degree of efficiency. Almquist and co-workers working with chicks (14) showed that for this species soybean protein is limited by deficiency of methionine. Hegsted and Stare (15) at Harvard found that although adult dogs could readily be kept in nitrogen balance (equilibrium) at a nitrogen intake of 2.5 to 3 grams per day when this nitrogen was furnished by the protein of skim milk powder, wheat germ or corn germ, they could not, however, be brought into such equilibrium when soybean flour or soybean grits furnished the nitrogen at an intake of 2.5, 3 or 3.5 grams per day.

There is considerable amount of evidence that the human species can satisfactorily digest and utilize soybean proteins. In one experiment (16) a group of 10 adults fed a 20 per cent soybean bread as the sole source of protein utilized the nitrogen to an extent of 80 per cent. Smith (17) at Wayne University, working with human subjects, found that the protein of autoclaved soybeans, soybean flour, and soybean milk had biological values of 96.5 per cent, 91.7 per cent, and 94.5 per cent, and digestibility values of 90 per cent, 93.9 per cent and 89.6 per cent, respectively.

Soybean milk has occupied a prominent place in the diet of Orientals for centuries. Tso (18, 19, 20) has contributed extensive information on the value of soybean milk as a substitute for cow's milk. Soybean milk has been used to a limited extent in the United States by infants and adults that are allergic to cow's milk. Clinical observations (21, 22, 23, 24) have shown that infants can grow and thrive for periods of over a year with this product as the sole source of protein in their diet and that it compares favorably with mammalian milk from the standpoint of availability and biological value of its protein.

The extensive investigations of Rose and associates at Illinois have shown that the question of protein requirements in nutrition is essentially a question of amino acid requirements. A protein lacking in any one of the nutritionally-essential amino acids in the diet of an animal results in nutritional failure, no matter how much is eaten. Amino acid requirements of animals, however, vary somewhat in different species. Were adequate data available on the amino acid content of different protein foods, it would be a relatively simple matter to ascertain their comparative protein values. However, any attempt at present to correlate with amino acid composition either the nutritive value of protein or their supplementary value is very unsatisfactory. Most of the data available on amino acid composition were obtained on isolated proteins and these values do not represent the foods as a whole from which the protein

were isolated. Furthermore, these values are too low in many cases because of unavoidable losses of amino acids involved in their recovery from the protein hydrolysates. Methods for determining amino acids in foods without isolating the protein are at present largely in the tentative stage.

Feeding experiments have shown (12, 25, 26) that addition of cystine or methionine to raw soybean meal improves its biological value. Addition of these amino acids to the cooked meal, however, effects little or no improvement. These results might indicate that soybeans contain enough cystine and methionine. Furthermore, chemical analysis (27, 29, 30) does not indicate a quantitative deficiency of cystine in soybean protein. The results of feeding experiments with rats and chicks show quite definitely that methionine is a growth-limiting deficiency in raw soybean protein (14, 8). The above considerations harmonize with Rose's hypothesis that cystine is not in itself an essential amino acid, but that it aids in making methionine more available when present in suboptimal amounts. Besides methionine there may be other less clearly defined amino acid limitations in the biological value of soybean protein which have not been revealed. These limitations may vary with species requirement. Almquist and coworkers (14) have reported that soybean meal made by a controlled heating process was slightly deficient in methionine, but was complete with respect to all other amino acids required by the chick.

The unusually wide range of differences in the physical characteristics of the large number of soybean varieties[1] raises the question whether there may be also differences in their protein nutritional values.

Determination of cystine, tryptophane, and tyrosine (29, 30) in glycinin, prepared from 10 varieties of soybeans (Peking, Illini, A. K., Manchu, Virginia, Mammoth Yellow, Haberlandt, Dunfield, Dixie, and Chiquita), selected on the merit of their widespread popularity among the growers in the United States, showed differences in the content of their amino acids greater than can well be attributed to experimental error involved in the analytical processes employed. The tryptophane values ranged from 1.89 per cent for the Mammoth Yellow variety to 2.84 per cent for the Illini variety. The cystine values ranged from 1.74 per cent for Illini variety to 1.46 per cent for the Chiquita variety. The Chiquita and Manchu varieties contained significantly higher percentages of cystine than the other varieties. The Illini variety which contained the highest percentage of tryptophane contained the lowest percentage of cystine, and the Chiquita variety, which was among the lowest in tryptophane, contained the highest percentage of cystine. The Peking and Dixie varieties were low in both cystine and tryptophane.

An important consideration when evaluating the nutritive properties of the protein of any food is the extent to which it can supplement the protein value of other foods. Conspicuous among foods that contain protein deficient in certain essential amino acids are the cereal grains. It has been estimated for prewar periods that about 36 per cent of the total protein used for human consumption in the United States was derived from cereal grains, chiefly from wheat (31). Were the amino acid deficiencies of this class of foods corrected by addition to them, in suitable proportions, of other protein foods rich in these amino acids, cereal grains could be utilized as a most important source of nutritionally adequate proteins at relatively low cost.

It has been amply demonstrated (11, 32, 33, 34, 8) that the proteins of soybean flour are valuable supplements for correcting the amino acid deficiencies of wheat flour.

Recently a mixture consisting of 5 parts of soybean flour and 95 parts of wheat flour was found not only to contain 19 per cent more protein than wheat flour alone but also to have twice its growth-promoting value (9). When the relative proportions were 10 and 90 the mixture showed practically the same value as skim milk powder and four times that of wheat flour alone. Even higher supplementing value for soybean flour, as compared with that of skim milk powder, has been reported (37).

Feeding experiments with rats and swine have been reported showing that properly cooked soybeans are valuable also as a supplement to corn (35, 36).

It is generally recognized that lysine is an outstanding amino acid deficiency in wheat flour. Available data leave little doubt that the protein of soybeans contains sufficient lysine to compensate for the deficiency of this amino acid in wheat flour. It also appears that wheat flour is low in threonine and valine as compared with soybean flour.

Osborne and Mendel (1) first showed that raw soybean meal as the sole source of protein in the diet will not support growth in rats at a satisfactory rate. Heating the meal in an electric oven at 110° for 4 hours failed to cause any significant improvement. However, after the meal had been heated with water for 3 hours on a steam bath and subsequently dried, the product promoted growth at a normal rate. Although heating ground soybeans in an electric oven causes little, if any,

[1] W. J. Morse of the Bureau of Plant Industry, U. S. Department of Agriculture, brought from the Orient samples of soybeans representing about 1,500 different types and varieties.

improvement in nutritive value, a considerable improvement has been observed (7) when the whole beans were heated in a sealed bomb. Apparently, in the latter case, sufficient of the original moisture content of the beans was preserved to effect the increase in nutritive value during heating.

That heated soybean protein is greatly superior to the raw protein has been confirmed by numerous investigators in studies with rats, swine, chicks, and other animals. Their conclusions were based on digestibility and metabolism studies as well as on gains in body weight (38, 28, 39, 35, 37, 40, 41, 42, 7, 43).

Considerable attention has been given to the question why heating soybeans improves the nutritive value of the proteins. The proteins of several legume seeds of the genus *Phaseolus* are limited in their nutritive value by a type of indigestibility which can be remedied by moist heat. The proteins of the navy bean (44), lima bean (45), Chinese and Georgia velvet bean (46), lentil (47) and cowpea (48) are rendered more digestible by heating with water. Rats will decline in weight rapidly and live for only 3 to 4 weeks when fed a diet containing either raw navy bean meal or its isolated proteins (49) as the sole source of protein in the diet. When the meal or its isolated proteins are first heated with water and then incorporated in the diet animals will barely maintain their weight. *In vitro* digestions of the proteins of the navy bean and velvet bean revealed marked increases in the amount of amino nitrogen liberated from the cooked bean proteins over that observed in case of the raw proteins (44). Although soybeans do not belong to the *Phaseolus* genus, the results obtained with *Phaseolus* beans suggest that the increase produced in the nutritive value of the soybean protein by heating may be also ascribed to improved digestibility. However, metabolism studies have been reported indicating that heating soybeans improves the digestibility of the proteins somewhat, but not to an extent commensurate with the improvement in general nutritive value.

The cooking of soybean meal evidently accomplishes two effects upon its protein nutritional value in the diet of rats; it makes the addition of cystine or methionine unnecessary, and it increases the growth-promoting value of the proteins two-fold or more. On the basis of these observations it might be concluded that, in the raw state, the soybean proteins are characterized by a type of indigestibility whereby certain amino acids are tied up in the protein molecule in such a way that they can not be assimilated. That cystine and methionine are not the only amino acids involved in this way is indicated by the fact that addition of cystine and methionine to raw soybean meal definitely improves its biological value, but only to about one-half the extent that cooking does.

Chemical studies on the isolated protein of the soybean have contributed material support to these conclusions (50). Unmistakable differences bewteen the behavior of raw and cooked protein were observed in digestion studies *in vitro* with trypsin. After parallel digestions of 100 grams each of raw and cooked protein for 96 hours, 63 grams of the raw protein remained in suspension as compared with 38 grams of the cooked protein. The 63-gram fraction of the raw protein retained 47 per cent of the total cystine of the original protein as against 33 per cent retained by the corresponding fraction of the cooked protein.

After removal of the solid fractions referred to, the liquid digests of the raw and cooked protein yielded on acidification another incompletely digested fraction from each of the digests. The fraction from the raw protein weighed nearly 6 grams and that from the cooked protein weighed 12 grams. All told, 69 per cent of the weight of the original raw protein was recovered from the digest in an incompletely digested form as against 50 per cent similarly recovered from the digest of the cooked protein. The partially digested fractions recovered from the digest of the raw protein retained 55 per cent of the total cystine as against 39 per cent for those of the cooked protein. The results show that the raw protein is not only less digestible than the cooked protein, but that a disproprotionate amount of the cystine is tied up in fractions largely resistant to digestion.

Cystine is liberated from the proteins of soybean with much greater difficulty than from other proteins studied. No free cystine could be detected in the digest of raw or cooked isolated soybean protein after 24 hours' tryptic digestion. Casein, similarly digested, yielded 80 per cent of its cystine. Soybean protein refluxed with 20 per cent HCl for 6 hours liberated only about two-thirds of the cystine present. Acid hydrolysis of casein, on the other hand, liberates 20 per cent of its cystine in 30 minutes, and all of it in 6 hours.

Although digestibility studies *in vitro* on the isolated proteins of the soybean reveal a difference in the behavior of the raw and cooked proteins toward the action of trypsin, the difference, however, does not run parallel with or entirely explain the marked improvement in biological value of soybean meal after it has been cooked. For instance, there was no difference in the rate of liberation of cystine from the raw and cooked proteins either on tryptic digestion or on acid hydrolysis. It appears that the superiority in nutritive value of cooked soybean meal can not be attributed entirely to an increased digestibility of the cooked meal protein.

Peanut proteins. Peanuts and soybeans have several characteristics in common. They are both legumes, they have a high content of protein and oil, and contain very little starch. Their proteins are also quite similar with respect to their chemical and physical properties.

The protein content of peanut kernels ranges from 28 to 35 per cent depending on the variety and locality where they are grown. About 82 per cent of the total nitrogen of the peanut is accounted for by two proteins, arachin and conarachin, which occur, respectively, in the ratio of about 3 to 1 (51). These proteins were first isolated and described in 1916 (52). Later, other investigations have been conducted on their chemical properties and amino acid composition (53, 54, 55, 56, 63, 64, 66).

The residue remaining after expressing the oil from peanuts is highly esteemed as a valuable protein concentrate for farm animals. Feeding experiments with rats (65) have demonstrated that peanut meal supplies protein that compares favorably in nutritive value with the best sources of plant proteins.

Although the total proteins of the peanut as represented in peanut meal and peanut flour have high nutritive value, arachin alone as the sole source of protein in the diet will not support satisfactory growth in young animals (64, 55). *In vitro* digestions with pepsin and trypsin show that it is not readily digestible (63). Unlike the proteins of soybeans and some other legume seeds, the digestibility of arachin is not appreciably improved by heating in the presence of water.

Analytical data indicate that arachin is deficient in methionine and tryptophane. These deficiencies have been confirmed by feeding experiments (55, 57, 58). Conarachin, on the other hand, contains an abundance of the amino acids that are deficient in arachin. A mixture of these two proteins in the same proportions that they occur in the peanut will enable young animals to grow at a very satisfactory rate (55). We have here an interesting illustration of protein supplementation within the same seed.

Peanut flour, which represents practically the total proteins of the peanut, offers a source of very good dietary protein for extending and partially replacing protein foods of animal origin. In a recent study on the comparative growth-promoting values of the proteins of peanut and soybean flours (9, 10), the interesting observation was made that, when fed at a 9 per cent level of protein in the diet, soybean protein promoted somewhat greater weight gains in rats than resulted with peanut protein fed at the same level. However, when fed at a higher protein level (15 per cent) peanut protein appeared definitely superior to that of the soybean.

Peanut meal is a valuable source of protein for supplementing the protein of corn (36). Zein, one of the chief proteins of corn, is deficient in arginine lysine, tryptophane, and cystine—amino acids that are well provided in the total proteins of the peanut. Peanut proteins also have a high value for supplementing the proteins of wheat flour (59, 60, 61, 62, 64).

Because of the limited production of peanut flour for human consumption this valuable source of plant protein has not been generally available in sufficient quantity to receive the recognition it merits.

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THE NUTRITIVE VALUE OF WHEAT GERM, CORN GERM, AND OAT PROTEINS

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It is the purpose of the present paper to discuss the proteins of wheat germ, corn germ, and of oats as substitutes for animal protein in human diets. Little reference is made to the proteins of other wheat or corn products, nor to the vitamin and mineral content of any of these foodstuffs, although it should be emphasized that, in any attempt to replace animal proteins in human dietaries by concentrates which contain high quality vegetable proteins, consideration must be given to the supply of other nutrients, such as the vitamins of the B-complex and minerals. On the whole, the available commercial concentrates and seed meals or flours which have been suggested as substitutes for animal proteins are good sources both of the B-complex vitamins and of minerals.

The proteins of wheat germ and corn germ are vegetable proteins of high nutritional value and commercial concentrates which contain them may be used to good advantage as substitutes for animal proteins. The germs of wheat and corn are by-products of the milling of the two main cereals of this country. They are generally included in varying amounts in those milling fractions known as "middlings" and "shorts," though they have been concentrated to some extent in animal feeds commonly called "wheat germ meal" and "corn germ meal." All of these products are used extensively in animal feeding. Preparation of wheat germ and corn germ for human consumption is at present carried out on a relatively small scale, but because of the size of the milling industry, considerable expansion of the production of these by-products should be possible. Such use should not seriously impair the supply for animal feeding because, according to Mitchell (1) the protein thus withdrawn can be amply replaced from sources unfit for human consumption or less well utilized by man.

Wheat germ and corn germ proteins. The nutritive value of wheat germ and corn germ proteins may be conveniently considered together. Only a few

data upon corn germ are available at the present time, chiefly because the most widely practiced method of milling corn does not yield a germ product suitable for human consumption. Wheat germ, on the other hand, has long been recognized as a product nutritionally superior to whole wheat although attention has been directed principally toward its high vitamin content. As a protein source, Osborne and Mendel (2) in 1919 concluded that the protein of the embryo was superior to that of whole wheat for the maintenance of adult rats and was somewhat superior to whole wheat for growth. Their reported protein value of 1.6 grams gain in body weight per gram of protein eaten appears somewhat low in the light of the work of Hove and Harrel (3) and may have been due to a less quantitative separation of the germ from other parts of the kernel than is now possible (table 1). It should be borne in mind that the nutritive value of various samples of wheat and corn germ will obviously be dependent upon the amount of actual germ they contain. Osborne and Mendel point out that the proteins of the embryo are markedly different chemically from those of the endosperm; 10 per cent may be removed as albumin by water extraction and 5 per cent as globulin by salt solution, whereas practically none is so removed from the endosperm.

Recent studies by Hove and Harrel (3) reported a biological value for wheat germ that is equal or superior to that of such animal proteins as skim milk, egg white, and casein. They further showed that wheat germ as the source of total protein in the diet of young rats gives growth equal to that obtained with casein, skim milk, or beef muscle. Wheat germ is also equal to these proteins as a supplement to two "poor-protein" diets. The protein of the first of these diets was supplied from plant sources selected to represent "an average American diet, plant sources" and that of the second by wheat gluten.

In a second paper, Hove and Harrel (4) report that skim milk and wheat germ are about equal in their ability to improve the nutritive value of white patent flour. Corn oil meal (corn germ) and soybean meal are somewhat less effective in this respect. Selected values taken from a chart in this paper are shown in table 2. All of these diets contained 10 per cent of protein supplied by various mixtures of flour and the supplemental proteins. Data obtained in the authors' laboratory (5) confirm this finding of the relative superiority of wheat germ as compared to corn germ as a supplement to white flour.

Data have also been obtained (5) upon the relative efficiency of skim milk powder, wheat germ, and corn germ in maintaining nitrogen balance in the adult dog. For this purpose the proteins of skim milk powder, wheat germ and corn germ are practically of equal value. Corn germ protein may be slightly superior to those of wheat germ and skim milk powder.

The biological value (per cent of ingested nitrogen retained) of defatted corn germ has been compared with defatted beef round by Mitchell and Beadles (1) using their modification of the Thomas method. It was shown that the protein is 85 per cent as digestible as the protein of beef round and has a biological value of 78, as high as that of beef round which was found to be 77.

For comparison, values of 50 to 65 for cereal grains, 51 to 60 for a series of nuts, 72 for the cashew nut, 94 for whole egg, 90 for raw whole milk, and 62 to 77 for various cuts of meat and animal organs,

TABLE 1

The nutritive value of corn germ, wheat germ and oat protein compared with other protein sources

PROTEIN SOURCE	PROTEIN IN DIET	PROTEIN* VALUE	AUTHOR
	per cent		
Commercial wheat embryo	13.7	1.60	Osborne and Mendel (2)
Commercial wheat embryo	6.95	1.61	Osborne and Mendel
Casein	11.0	2.46	Osborne and Mendel
Lactalbumin	10.3	2.44	Osborne and Mendel
Wheat germ	4.7	2.12	Hove and Harrel (3)
Wheat germ	10.2	2.79	Hove and Harrel
Egg white	4.7	2.02	Hove and Harrel
Egg white	10.0	2.58	Hove and Harrel
Skim milk	5.4	1.83	Hove and Harrel
Skim milk	10.7	2.85	Hove and Harrel
Corn oil meal (corn germ)	10.0	2.40	Hove and Harrel (4)
Soybean oil meal	10.0	1.97	Hove and Harrel
Corn germ (solvent extracted)	10.0	1.8	Block and Bolling (6)
Corn germ (hot expulsion)	10.0	2.1	Block and Bolling
Whole milk	10.0	1.9	Block and Bolling
Whole oats	10.0	1.17	Osborne and Mendel (8)
Whole oats	8.0	1.39	Osborne and Mendel
Whole wheat	10.0	1.40	Osborne and Mendel
Rolled oats	10.0	1.52	Stewart et al. (10)
Dried oatmeal	10.1	1.55	Stewart et al.
Oven expanded cereal†	9.5	1.60	Stewart et al.
Puffed oats‡	9.8	0.37	Stewart et al.

* Protein value = grams gain per gram of protein eaten.

† Oven expanded oat cereal made by cooking oat flour in dough form in a jacketed tube under pressure of 100 lb. for 1 to 2 minutes, forming into globules and expanding the globules in approximately 1 to 2 minutes in an oven held at 200°C.

‡ Puffed oats made by preheating oat groats for 5 minutes to a temperature of 122°C. and then subjecting the groats to live steam up to 200 lbs. 198°C. in 2 minutes and finally puffing by releasing the pressure suddenly. This latter product has been sold in limited amounts here and in Canada.

are given. The biological value of soybeans is given as 67.5.

Data on the amino acid content of the proteins of wheat germ and corn germ have recently been presented by Block and Bolling (6). The content of the essential amino acids compares favorably with excellent proteins such as milk and meat. These comparisons are shown in table 3.

It appears evident from the available studies that the proteins of these germs must be considered as essentially the equivalent of first-class

TABLE 2

The value of wheat germ and corn germ proteins as supplements to white patent flour

PROTEIN SUPPLEMENT	PER CENT OF TOTAL PROTEIN FROM SUPPLEMENT	PROTEIN* VALUE	PER CENT OF TOTAL PROTEIN FROM SUPPLEMENT	PROTEIN* VALUE
None	0	0.78		
Dry skim milk	20	1.45	50	2.26
Defatted wheat germ	20	1.52	50	2.26
Corn oil meal	20	1.13	50	1.71
Soybean oil meal	20	1.23	50	1.77

* Grams gain per gram of protein eaten.

TABLE 3

Percentage composition of corn and wheat germ proteins compared to milk and muscle (Calculated to 16 per cent of nitrogen)

AMINO ACID	CORN GERM	WHEAT GERM	COW'S MILK	MUSCLE
Arginine	6.8	6.0	4.3	7.1
Histidine	2.7	2.5	2.5	2.2
Lysine	5.8	5.5	7.5	8.1
Tyrosine	4.9	3.8	5.3	3.1
Tryptophane	1.3	1.0	1.6	1.2
Phenylalanine	5.6	4.2	5.7	4.5
Cystine	1.2	0.6	1.2	1.1
Methionine	2.6	2.0	2.8	3.3
Threonine	4.4	3.8	4.6	5.2
Leucine	16.3 ±3.1	7.4 ±2.3*	16.2 ±3.1	12.1 ±1.1
Isoleucine	3.7 ±0.4	3.0 ±0.5*	4.4 ±0.4	3.4 ±0.2
Valine	5.8 ±1.2	4.1 ±1.0*	4.5 ±0.4	3.4 ±0.4

* Personal communication from Dr. R. J. Block.

animal proteins, both when used as the sole source of protein or as protein supplements in the diet. The protein content (wheat germ 25–35 per cent; corn germ 13–25 per cent) is sufficiently high to make their inclusion in the dietary worth while. Such problems as those of stability, rancidity, and palatability may apparently be overcome by toasting, or more satisfactorily by extraction with a fat solvent.

Present methods of milling yield approximately 0.5 per cent of the wheat as wheat germ, although wheat actually contains close to 3 per cent of germ. This indicates a potential germ production of at least 150 million pounds of wheat germ per year, which might be tripled by more efficient separation. The present annual production is estimated to be from 30 to 50 million pounds. (For comparison, there were 500 million pounds of dry skim milk powder produced in the United States during 1941.)

Corn germ is a by-product of essentially two different types of milling, "the wet milling industry" represented by the manufacturers of starch, and the "dry milling industry" which produces hominy products. The germ recovered in the wet milling industry is said to be unsuited for human consumption. Sulfurous acid is used in the process and renders the germ unpalatable and probably destroys some of its nutritive value as well. The oil is extracted from this germ and the pressed germ cake is used in animal feeds. The dry milling industry probably recovers about 45 million pounds of dry corn germ per year. It has been estimated that 600 million pounds of defatted, palatable corn germ could be produced.

Oat protein. Relatively few data are available upon the efficacy of oat proteins in nutrition. Some of the early reports may be looked upon with suspicion since adequate rations with respect to vitamins and minerals were not always used. In his review on the biological values of proteins, Mitchell (7) gives values of 60 for maize, 65 for oats, 67 for wheat, 77 for rice, and 64 for barley; and he expresses the opinion that differences of this magnitude are probably of little if any significance. Early studies by Osborne and Mendel (8) indicated that neither maize nor oats is adequate as a sole source of protein for the rat, while rice and barley proteins, in contrast, were reported as adequate at a level of 16 to 17 per cent of protein in the diet. Sherman, Winters and Phillips (9), in balance studies on human volunteers, reported oats and maize to be essentially equal in value as sole sources of protein. Nitrogen balance was not maintained by these proteins when they were fed at daily levels of 0.49 to 0.55 gram of protein per kilogram of body weight although similar levels of protein, of which 8 to 20 per cent was supplied by milk, were adequate.

A recent paper by Stewart, Hensley, and Peters (10) reports studies on the nutritive value of the proteins of rolled oats and oat cereals as determined by the method of Osborne, Mendel, and Ferry (11). Selected figures from this paper and those obtained by Osborne and Mendel are shown in table 1. Home-cooked oatmeal and the oven-expanded cereal appear to have suffered no loss in protein efficiency, although puffed oats are clearly inferior in protein quality.

Stewart et al. state that "nutritionists have

recognized the superior quality of oat protein," and there seems to be a popular idea that oats are superior to other grains. The data available indicate that oat proteins are essentially the equivalent of other whole grain proteins and are distinctly inferior to the proteins of wheat germ and corn germ. Since oats are usually consumed as whole grain products, they supply more nutritive value in the form of proteins, vitamins, and minerals than highly refined cereals.

SUMMARY. The proteins of wheat germ and corn germ are of high nutritive value. As the sole source of protein for the growing rat, they compare favorably with the proteins of skim milk powder. As the sole source of protein for the adult dog they maintain nitrogen balance when fed at the same level as is required in the case of skim milk protein. Wheat germ is superior to corn germ as a supplement to white flour and compares favorably to skim milk powder. In rat experiments, defatted corn germ has a digestibility of 85 per cent as compared with defatted beef round of 99.7 per cent, but its biological value is equal to beef round at a value of 77. These germ proteins are by-products of our large milling industry. They could be prepared in large amounts and in ways such that they have satisfactory stability and palatability. Oat protein compares favorably with the protein of other whole grain cereals but is inferior to the proteins of wheat and corn germ. These proteins should be valuable in any national or international protein shortage, the germ proteins because they compare favorably with animal proteins, and the oat proteins as the equivalent of any other member of the whole grain cereals.

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THE NUTRITIVE VALUE OF YEAST PROTEINS

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Since the beginning of this century dried yeast has been recognized as a valuable high-protein food. It is especially promising in emergency conditions because it is produced at an extremely rapid rate and at a low cost compared to animal proteins (1). Furthermore, yeast is an excellent source of vitamins as well as of high grade protein. It is not surprising, therefore, that during the last World War dried yeast was employed in large quantities as a livestock feed and in smaller amounts in human dietaries. During the present conflict the necessity for developing additional sources of high quality protein has led to a renewed interest in the biological value of yeast protein with especial reference to human nutrition.

Dried brewers' yeast is a readily available source of yeast protein. However, the annual yeast production of the brewing industry in this country (equivalent to about 30,000,000 pounds of dried yeast or 14,000,000 pounds of protein) is only a fraction of the quantity which would be needed if yeast were to furnish an appreciable portion of the protein of human food. Furthermore, brewers' yeast must be debittered for human consumption and a certain proportion of the vitamin content is lost in this process.

The possibility of producing yeast for human consumption from other types of yeast has been investigated by several workers, and yeasts of the genus *Torula* have afforded very promising results. These yeasts grow in the absence of organic nitrogen which is an important factor. Hayduck (2) in 1915 reported on the use of *Torula* in the commercial production of a "mineral yeast." Thaysen (1) in 1940 undertook an extensive investigation of *Torula* yeasts and succeeded in developing a new strain—*Torulopsis utilis* var. *thermophil.*—which grows extremely rapidly (fifteen-fold weight increase in 9 hrs.) and will tolerate higher temperatures than other strains. The latter factor is of

considerable economic importance in growing the yeast in tropical climates. The processed yeast is obtained in the form of light yellow flakes with a meaty or nutty taste and is called "Food Yeast." The production of food yeast is receiving considerable attention both by the British and in this country, and enormous quantities of the material could be produced if it became desirable to do so.

The literature concerning yeast proteins will be discussed under the following heads:

I. Chemical composition of yeast and yeast proteins
II. Nutritional value
  A. For the rat
  B. For the dog
  C. For man
III. Yeast as a fodder

No attempt will be made to cover all of the papers which have appeared in this field, but rather to select those articles which have a significant bearing on the problem of the nutritive value of yeast proteins.

I. *Chemical composition of yeast and yeast proteins.* Dried brewers' yeasts vary somewhat in composition, but the figures generally fall within a rather narrow range. The following is a typical proximate analysis representing the average of a large number of samples (3).

Crude protein (N × 6.25)	47.6
Carbohydrate	32.6
Fat	1.0
Fiber	0.8
Ash	8.4

Although analytical figures on *Torula* yeasts are not complete, the available data indicate that they have approximately the same composition as brewers' yeast.

Yeast contains a variety of non-protein nitrogenous constituents including purines, pyrimidines, choline, glucosamine, glutathione, etc. Purines account for 8–13 per cent of the total nitrogen (4, 5), pyrimidines 4 per cent (4), choline 0.5 per cent (4) and glucosamine 0.5 per cent (4).

Crude protein of dried yeast usually varies between 45 and 55 per cent although both higher and lower figures are reported. The crude protein values are calculated from the total nitrogen and hence are 12–18 per cent high due to the presence of the large amounts of non-protein nitrogen in yeast. Von Soden and Dirr (6) concluded, from studies of amino nitrogen in enzymatic hydrolysates of yeast, that only 80 per cent of the total nitrogen of yeast was actually protein nitrogen.

Attempts to isolate and characterize yeast proteins have not proven very successful. Only a part of the nitrogen can be extracted from yeast even by dilute alkali after defatting or rupturing the cell membrane (7). Furthermore yeast cells autolyze rapidly with consequent alteration in the chemical nature and solubility relationships of the proteins. Dreyer (8) obtained 65.7 per cent of the total nitrogen on extracting yeast with 10 per cent ammonium carbonate and reported that the extract contained an albumin and a globulin. Thomas (9, 10, 11) separated from autolyzed yeast a heat-coagulable albumin and a non-coagulable para-nucleoprotein which was sparingly soluble in 10 per cent sodium chloride. More recently, reports by Csonka (7), Strain (12), and Kazakov (13) indicate that extraction of defatted or ground yeast with water removes a thermolabile and a thermostable protein. Subsequent extraction with dilute salt solution removes a globulin. And finally, a further amount of protein is obtained by extraction with dilute alkali. Csonka (7) states that all of these fractions consist of nucleoprotein. In view of the rapid autolysis of yeast protein, it is not certain what relation the various protein fractions have to the proteins present in the living yeast cell.

Amino acid analyses have been made on whole yeast and on various protein fractions. The latter data have little significance since they depend on the method of preparation of the particular material under investigation. They will be included in the references but will not be discussed further.

Since pure yeast proteins are not available for analysis the method of expressing the results is somewhat complicated. In some cases the values have been calculated as per cent of amino acid in dried yeast. This method is unsatisfactory since the per cent of protein in dried yeast varies from sample to sample. Other authors have reported amino acid nitrogen as per cent of the total nitrogen. This method seems to be more satisfactory and other figures have been recalculated to this basis wherever possible. The amino acid analyses of whole dried yeast are summarized in table 1.

In addition to the data recorded in table 1, isolated analyses have been reported on individual amino acids of whole yeast. Csonka (7) found that dried brewers' yeast contains 0.3 per cent of cystine 1.37 per cent of arginine, and 2.61 per cent of lysine, while dried bakers' yeast contains 0.27 per cent, 1.32 per cent, and 2.15 per cent respectively of these three amino acids. Woolley and Peterson (17) reported that dried bakers' yeast contains 1.03 per cent of histidine and noted that acid-hydrolyzed yeast contains substances which interfere with the Kapeller-Adler test for that amino acid. Prunty (18) obtained values of 0.92 and 0.52 per cent cystine in two samples of dried brewers' yeast. Tomado (19) found 1.6 per cent of tryptophane in a sample of *Saccharomyces sake* which he analyzed. Dirr and von Soden (20) have published a recent paper on amino acid analysis of yeast. Unfortunately neither the original paper nor an abstract of it are available. Thomas (9, 10,

11), Csonka (7), and Kiesel (21) have reported amino acid analyses on various protein fractions isolated from brewers' yeast. Kazakov (13) determined the content of several of the essential amino acids in three protein fractions isolated from *Torula* yeasts. The original paper is not available and the abstract reports figures only for tryptophane, which was found to make up 0.88, 0.43, and 0.72 per cent respectively of the three proteins. Kazakov states that *Torula* yeast contains all of the essential amino acids.

Excluding Meisenheimer's early results which, for the most part, can be considered as little more than qualitative, the figures of the more recent investigators agree as well as could be expected.

TABLE 1

Amino acid nitrogen content of dried yeast (Per cent of the total nitrogen)

AMINO ACID	A	B	C	D
Valine	10.0	3.3		
Isoleucine		2.3		
Leucine	5.0	8.8		
Threonine		3.7		
Methionine		+		
Phenylalanine	8.0	2.2		
Tryptophane	0.5	1.2	0.9	1.3
Tyrosine	2.0	2.0	2.5	2.9
Lysine	10.0	7.7	11.4	11.6
Histidine	5.0	4.7	4.1	5.3
Arginine	5.0	8.7	11.3	10.9
Cystine	2.0	0.9	1.6	1.7
Glycine	0.5			
Alanine	10.0			
Aspartic acid	3.5			
Glutamic acid	6.0			
Proline	2.0			
Hydroxyproline	4.5			
Sulfur		0.9		

A. Meisenheimer (4); brewers' yeast
B. Block and Bolling (14); type of yeast not specified. Results recalculated to above basis
C. Kraut and Schlottmann (15); brewers' yeast
D. Fink and Just (16); *Torula yeast*

As a matter of fact, Fink and Just (16) and others have noted a considerable variation in amino acid content of yeast samples of the same type grown under slightly different conditions. Evidently the composition of yeast protein is not as constant as that of animal protein.

The most comprehensive recent analysis of the amino acid content of yeast protein is that of Block and Bolling (14). These authors expressed their results as per cent of amino acid in a theoretical yeast protein containing 16 per cent nitrogen. Since the analyses were made on whole yeast it seems a safe assumption that crude protein (N × 6.25) was used as the basis for the calculations. In order to compare the amino acid composition of yeast with that of animal proteins, the figures of Block and Bolling for yeast protein and muscle protein and a compilation of data on the amino acid content of casein are given in table 2. Since casein contains approximately 16 per cent nitrogen the figures are comparable with those of Block and Bolling.

These amino acid analyses of yeast protein are incomplete and are admittedly not highly accurate in certain instances. Nevertheless they definitely establish that yeast protein contains all of the essential amino acids and is a biologically complete protein. Whether the essential amino acids are present in the proper proportions for maximum utilization by the animal body can hardly be decided on the basis of the present data. It is possible that yeast is deficient in sulfur-containing amino acids and this possibility is supported by feeding

TABLE 2

Percentage composition of yeast protein, muscle protein* and casein***

	CRUDE PROTEIN OF YEAST	MUSCLE PROTEIN	CASEIN
Arginine	4.3	7.1	3.79†
Histidine	2.8	2.2	1.81†
Lysine	6.4	8.1	6.20†
Tyrosine	4.2	3.1	6.01†
Tryptophane	1.4	1.2	1.11†
Phenylalanine	4.1	4.5	5.00¶
Cystine	1.3	1.1	0.26†
Methionine	+	3.3	3.10†
Threonine	5.0	5.2	4.40‡
Leucine	13.2 ±2.6	12.1 ±1.1	12.10§
Isoleucine	3.4 ±0.2	3.4 ±0.2	—
Valine	4.4 ±0.8	3.4 ±0.4	7.00§

* Block and Bolling (14).
** Compilation of recent data.
† Beach, et al. (22).
‡ Winnick (23).
§ Fromageot and Mourgue (24).
¶ Kapeller-Adler (25).

experiments to be reported in the next section. However, an inspection of table 2 reveals a striking similarity in the amino acid composition of yeast and that of casein and of muscle protein. On the basis of chemical analysis, therefore, yeast protein should possess a high biological value.

In addition to the amino acid figures, certain other analytical data may have a pertinent bearing on the question of the nutritive value of yeast protein. The presence of a large amount of non-protein nitrogen in yeast is of interest in evaluating feeding experiments. Obviously the crude protein of yeast, as calculated from the total nitrogen, is considerably higher than the actual protein content. Yet this fact has not been taken into account in planning feeding experiments or in calculating biological values of yeast proteins.

The high purine content of yeast is also of interest to the nutritionist. Obviously the ingestion of large quantities of yeast by man would result in the production and excretion of considerable amounts of uric acid, and this might be deleterious in certain conditions. This point will be discussed further in a later section.

Yeast has a high ash content and the distribution of the various constituents of the ash is unique. Potassium and phosphorus are unusually high, whereas calcium, sodium, and chloride are very low. The high-phosphorus low-calcium content of yeast may well be responsible for the fact that pigs receiving a large amount of yeast in their diet may develop rickets (26). Furthermore the possible effects of the phosphorus on the acid-base economy of the body must be considered.

II. *Nutritional value of yeast proteins.* A. *For the rat.* The nutritive value of yeast proteins will be discussed under the three topics, digestibility, growth studies, and biological value. Only those experiments will be considered in which the yeast protein contributed significantly to the protein nutrition of the animal.

1. *Digestibility.* Völtz (27) reported that the digestibility of brewers' yeast was 88 per cent and that 94 per cent of the caloric value of the yeast was utilized by the rat. Osborne and Mendel (28) found that brewers' yeast was utilized to the extent of 74–83 per cent and Still and Koch (29) reported a value of 72 per cent. Mitchell (30) obtained coefficients of digestibility of 78 and 76 per cent respectively at 5 and 10 per cent levels of yeast in the diet.

There seems to be general agreement that yeast protein is readily digested and absorbed by the rat.

2. *Growth studies.* There have been several reports that yeast protein supports normal growth in rats. Osborne and Mendel (28) fed brewers' yeast as the sole source of protein at levels of 30 and 40 per cent. Rats were maintained for more than a year on these diets without ill effects. Those on the 40 per cent level grew at a normal rate, those on the 30 per cent level somewhat less rapidly. Nelson, Heller, and Fulmer (31) fed to rats diets containing 25–50 per cent of dried brewers' yeast. At a 45 per cent level, normal growth and reproduction occurred. Three generations of rats were reared on these diets, the growth rate of the offspring being slightly below normal. At the 50 per cent level the growth rates flattened out after three months. Mangold, Columbus, and Hock (32) have reported quite similar results with a *Torula* yeast grown on sulfite wastes. Willimott and Wokes (33) reported that a diet containing 50 per cent of saline extracted yeast supported normal growth in rats.

In contrast to these results are others indicating that yeast protein is not as effective as casein or other animal proteins in promoting growth of rats. Still and Koch (29) made a careful study of bakers' yeast. They reported that rats on diets containing 38 per cent of bakers' yeast as the sole source of protein grew at a subnormal rate and concluded that all of the yeast protein was not readily utilized by the rat. These workers made no allowance for the non-protein nitrogen content of the yeast.

Hock and co-workers (34–37) have recently published several papers dealing with the supplementary effects of cereal protein, *Torula* or brewers' yeast, and fishmeal. In each of the diets, about one-sixth of the protein was provided by a mixture of rye and wheat. The remainder of the protein consisted of yeast and fishmeal in varying proportions. When only yeast was added, the rats grew only half as rapidly as when the remainder of the protein consisted entirely of fishmeal. However, normal growth was obtained when 50 per cent of the fishmeal was replaced by yeast. These results indicate that yeast has a lower nutritive value than fishmeal for the rat. In the most recent report of this series Hock and Fink (37) show that the addition of 2 per cent of *l*-cystine to yeast markedly increases its nutritive value.

Kon and Markuze (38) reported that the growth rate of rats on a brewers' yeast diet was improved by replacing a part of the yeast with wheat flour.

3. *Biological value.* Still and Koch (29) report a biological value of 45 per cent for brewers' yeast protein. Mitchell (39) found that yeast, fed at a 5 per cent level, was completely utilized and reported a biological value of 85 for the yeast protein.

B. *For the dog.* There seems to be general agreement that yeast is a satisfactory source of protein for the dog. Völtz (40, 41) found an 83.6 per cent utilization of yeast nitrogen by the dog, Rubner (42) 98 per cent, Deutschland (43) 83–89 per cent and Karr (44) 80 per cent.

C. *For man.* There is very little significant data in the literature concerning the nutritive value of yeast proteins for man. The earlier studies were concerned mainly with determining how much yeast could be tolerated in the human diet (45, 46, 47). It was found that dried yeast in quantities up to 100 grams produced no ill effects with the exception of one or two subjects who suffered from diarrhea. Even the more recent experiments have dealt for the most part with the digestibility of yeast. Thus Kuen and Püringer (48) reported that 90 per cent of the nitrogen of dried bakers' yeast was digested and absorbed, whereas fresh bakers' yeast was poorly utilized. Dirr (49) fed two male and two female subjects diets containing 87–100 grams of protein, 65 grams in the form of yeast, and found that the yeast protein was absorbed almost as well as animal protein.

Nitrogen balance studies have been made in

only a few instances. Funk, Lyle and McCaskey (50) maintained four men on diets in which all of the protein was provided by yeast. The subjects showed a negative nitrogen balance on an intake of 6.5 grams of yeast nitrogen. The same amount of nitrogen in the form of potatoes maintained the subjects in nitrogen balance. Funk observed that the fecal nitrogen increased on the yeast diets. Bickel (51) determined the supplementary effect of various proteins added to a standard diet affording 0.9–1.0 gram of protein per kilo of body weight. The addition of 7.6 grams of casein brought the subjects into nitrogen balance while 30 grams of yeast protein were required to do so. In a subsequent paper, Bickel (52) reported that yeast protein was well absorbed but that the nitrogen retention with yeast protein was inferior to that with meat, milk, or egg protein.

Although these data are obviously inconclusive they indicate that yeast may be somewhat inferior to animal proteins in human nutrition.

Another aspect of this problem is the effect of yeast feeding on blood and urine uric acid. Several workers have reported no increase in blood uric acid following administration of yeast (53, 54, 55). However, these experiments were of short duration or involved rather small quantities of yeast. Those investigators who fed large quantities of yeast to human subjects for several days have usually reported an increase in blood uric acid (49, 50, 56). Dirr (49) also noted increases in blood pressure and creatinine.

The data on nutritive value of yeast proteins for man are fragmentary and not always consistent. It is not possible to reach any broad conclusions as to the potential importance of yeast as a source of protein for human diets. However the available data indicate that yeast protein is somewhat inferior to animal protein in human nutrition and that a thorough study of the effects of long-continued yeast ingestion on blood constituents is an essential prerequisite for any recommendation concerning the inclusion of large amounts of yeast in human dietaries.

III. *Yeast as a fodder.* The value of yeast as a fodder for livestock has been reviewed in great detail by Braude (3).

In the last few years comprehensive experiments have been carried out in Germany on the feeding of yeast to pigs (57–60) and to cattle (61, 62, 63). These experiments showed that pigs could be fattened very satisfactorily on diets whose sole source of protein was yeast. *Torula* and brewers' yeast were equally effective. However growing pigs showed superior gains when part of their dietary protein was of animal origin. Recently Macrae, El-Sadr, and Sellers (64) reported that the protein of *Torula utilis* yeast is as effective as casein in supplementing maize proteins in the diet of the pig. In the case of cows, yeast was fed at a level of 1.7–2.18 kgm. per head per day. This resulted in an increased production of high quality milk.

Axelson (65) has reported extensive observations showing that yeast may supply 50 per cent of the protein requirement of poultry. He also found that dried yeast could replace the protein of oil cakes for horses.

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INCREASING THE USE OF PLANT PROTEINS[1]

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Plant proteins play a vital part in the economy of the world whether that world is at peace or involved in war. Proteins themselves play a vital part in the word's food picture since they are essential and scarce nutrients. Without protein in reasonable amounts we cannot expect permanent peace any more than we can expect this peace without sufficient calories to keep men from starvation.

A war could not be fought in the present age if men had not learned to make good use of plant proteins. With the exception of America, no major nation has the natural resources to feed either its armies or its civilian populations upon a diet rich in proteins of animal origin.

Due to the fact that more people can live per acre in a densely populated area if they use plant proteins, the oriental nations have long learned to thrive upon a minimum of animal protein. Today the Japanese army is fighting upon a ration that draws its protein primarily from plant sources with a small supplement of those from meat and milk. Among the captured Japanese foodstuffs are found enriched white flour, dried beans and peas, brown rice, seaweed, and dried yeast with small amounts of dried fish, canned milk and canned meat. These plant foods simplify the operations of the Japahese army because they are easy to store, transport and cook in contrast to meats that must either be refrigerated, canned or dried.

Likewise, the Russian and German armies are making extensive use of dark, heavy breads, peas, beans, buckwheat, soybeans and such special products as dry yeast.

The typical modern American eats two slices of bread at each meal. This is his major source of plant protein. This same bread consumption is continued when men enter the armed forces. Thus each man eats about five or six ounces of bread per day. In exceptional cases such as field duty this amount may rise sharply and men may eat twice this amount. When men first enter the armed services they tend to increase in weight. Since they are usually allowed all the bread they wish, they may eat large amounts for the first two weeks. This is especially true of the colored men from the south who are fond of bread. The Navy's allowance for bread is twelve ounces daily per man or the equivalent in flour. Only about half this amount is really used. Supply officers use this saving effected in bread to buy more milk or vegetables in many cases.

The improvement of the protein quality of wheat

[1] The material in this article should be construed only as the personal opinion of the writer and not as representing the opinion of the Navy Department officially.

bread by the inclusion of such supplements as dry skim milk, soy flour, dry brewer's yeast, wheat germ or corn germ is accepted today. Thus far not much use has been made of these findings in feeding the armed forces. The traditional outlook of those in charge of feeding operations is conditioned by the large amount of meat given men in the armed services. Older supply officers usually assume that there is no need for improving the protein quality of bread since meat affords an adequate supplement. The addition to bread of such other products as whole wheat flour or soya flour increases the list of items that must be carried in stores. It also complicates the baking operations.

However, this point of view concerning the maintenance of the status quo in the composition of bread is not universal. One large marine bakery has been making extensive use of soya flour for several years in both breads and cookies. By one means or another many alert supply officers are finding means of procuring rye flour, whole wheat and soya flours.

The older viewpoint in the armed services concerning the futility of improving bread proteins may be yielding to a newer point of view for several reasons: (1) A small minority of men depend upon bread as the main item of their diet; (2) a variety of breads makes meals more acceptable; (3) under some conditions meat supplies may fail and bread be the important item of food. The newer viewpoint assumes that bread should have the highest possible quality in terms of proteins, minerals, and vitamins.

Furthermore, the time will soon come when nutritionists in the armed services must assume new responsibilities. The number of patients and workers in hospitals is bound to increase enormously while the number of men in training camps and stations will decline. The sedentary lives of those fed in hospitals means that the type of food must change from that fed in camps. Fewer calories will be required. Less fried foods can be tolerated. More fruits and salads will be needed. In general the variety of foods offered must be greater although the amount will be less. This means that the quality of every item offered should be the best that can be produced economically. For this reason the best possible combinations of proteins should be used in breads and pastries. This provides insurance for that patient who may select diets low in meat or milk and eggs.

Not only should bread be improved but also other cereal items such as hot cakes, doughnuts, cookies, pies, and breakfast foods. Astounding amounts of doughnuts, cookies, and pies are consumed both in the regular messes of the armed services and in separate eating places such as Ship's Service and Post Exchange. Since the minority that do not adapt themselves readily to the messes of the Army and Navy tend to buy foods outside, the composition of these foods is especially important. Since proteins of animal origin are sold very little in these outside feeding operations, the quality of the protein of the cakes and cookies is very important in the welfare of a small group of men and women.

The problem of the extent to which Americans should consume more plant proteins and less of those of animal origin faces the nation today. American will always be interested in the use of meat because we have vast areas of land that are only suitable for ranges. On the other hand, we can produce either animal or plant proteins in large areas such as the corn belt.

The thinking man realizes that several men can be fed for every one now fed by the grains of the corn belt if we abandon part of our swine feeding industry. However, the typical American feels that the hungry European is far away. He says "export the soybeans and leave me my pork chops." In other words, the problem appears unreal.

However, some progress is being made in increasing the utilization of soybeans, dry brewer's yeast, and germ proteins as primary foods in our diets. With the great progress in biochemistry, there is no reason that our nation cannot consume more plant foods with the maintenance of adequate nutrition. At the same time the future will undoubtedly see flavors developed in such products as soybeans and yeast that will make them able to compete with beefsteak and meat products. Only a beginning has been made in producing the flavors in such products as soya sauce which is so widely used in the orient to improve the flat tastes of plant products.

In times of war we hear a great deal of the value of reserves of minerals, reserves of manufacturing plants, reserves of scientists and even reserves of foods. The ability to use plant proteins effectively constitutes a reserve that is seldom discussed. It takes little imagination to perceive the asset of being able to rely upon large amounts of plant proteins in periods of national emergency. The biochemist plays his part in providing adequate knowledge concerning nutritive values and methods for producing acceptable flavors and methods of cookery. Some experience in cookery and in modifying national food habits on a large scale is also essential if this reserve is to be made effective in a short time in case of need.

No one can deny the economy of the use of plant proteins but also no one can anticipate the willingness of the American public to change its food habits. The more the nutritionist knows about the composition of plant products the more assurance he can give that adequate diets can be constructed with a base of plant foods. Furthermore, partof the

future of plant proteins lies in the hands of the researcher in biochemistry because he has the means for discovering the methods of producing pleasing flavors by both chemical and microbiological methods.

In our thinking today we tend to center our attention on producing enough food for ourselves and other nations. Another aspect of the problem may arise in more peaceful times. A farmer can feed a given number of people by laboring the year around to produce corn and soybeans for swine feed. He can feed the same number of people with about one-third the time and labor if the people eat the plant products. Under such a condition the farmer would have two-thirds of his time for leisure and maintain the same number of men upon the plant foods. Today such a point of view is visionary. Tomorrow it may not be.

Many nutritionists are overoptimistic concerning the savings in human foodstuffs that can be made by changing the public food habits to a diet lower in meat and eggs. In 1942 the estimated consumption in the United States of protein from meat and eggs was about 3.8 billion pounds.[2] This might be reduced by one-third without too severe reprecussions on the part of either agriculture or the consumer. Morrison[3] estimates the protein produced from an acre of land in the form of pork amounts to 22.7 pounds annually while that in the form of soybeans amounts to 294.7 pounds. The therms of energy produced amount to 672.9 for pork and 1,534 for soybeans or 3,124 for corn. The most that could be assumed if men turned from pork to soybeans for a third of their protein would be that abourt thirteen times as many people could be provided with protein from an acre of land. A more realistic figure is probably four or five which credits swine with their great efficiency in calory production and the conversion of corn into calories more suitable than those of corn for human consumption. Likewise the usefulness of swine and chickens in converting such waste products as meat scrap into meat for human consumption would be credited in part.

The number of additional people that could be fed if the whole population of the United States were willing to exchange a third of their proteins from meat and milk for that from soybeans would run from ten to thirty millions.

In conclusion we cannot doubt the greater efficiency of partly maintaining a population on plant products. Our armed services are beginning to make use of plant proteins such as those of soya flour for supplementing bread and pastries. Maximum safety is attained in nutrition when every important food item, such as bread, is given the highest qualitative value that can be attained practically. Because the ration of the Army and Navy is rich in meat seems no reason to neglect the quality of bread protein. The increased knowledge of the biochemist will ultimately insure the adequacy of diets based on plant proteins. Research will also provide more pleasing flavors. No one, however, can anticipate the trends of human food consumption by populations not faced by severe emergencies. The American public may realize that they can feed more starving peoples in foreign lands if they shift toward a vegetarian diet but there is little indication that they will do so without compulsion. The knowledge and ability to utilize plant proteins effectively is in itself a source of reserve strength for America in times of emergency. In times of peace it may prove a means of giving the hard working farmer some additional leisure.

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[2] Report of U. S. Tariff Commission, February 1944.

[3] Morrison, F. B. Feeds and Feeding, Pg. 158, 1936.

INTERIM REPORT SUBMITTED BY THE SECRETARY OF THE AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, INC.

Report of Council Meeting May 11–12, 1944. A meeting of the Council, held in St. Louis, Mo., May 11–12, 1944, was attended by all members of the Council.

In addition to the routine business of the Society, the Council discussed the activities of the Committee on National Defense and the results of the questionnaire sent to members last year. The officers of the Society were directed to take further specific steps to increase the usefulness of biochemists in the present emergency. The members will be advised of these in detail.

The Council directed the Secretary to conduct an election of new members as well as the annual election of officers by mail.

Plans for the Federation Meeting to be held in Cleveland, Ohio, next spring were decided.

The dues for the next year were continued at $2.50.

Dr. R. J. Anderson, as Managing Editor of the Journal, reported its financial condition very satisfactory, the past year's operations having made a profit, instead of a loss as in the previous year. Publication of the next volume of the Cumulative Index, and publication of the History of the Society as authorized last year by the Council are under way but not completed.

The President appointed Dr. G. O. Burr to finish the unexpired term of Col. Paul E. Howe as representative of the Society in the Division of Biology and Agriculture of the National Research Council.

The Council heard with regret of the deaths of the following members:

Henry Gray Barbour
Russell H. Chittenden
E. P. Clark
C. Stuart Gager
Yandell Henderson
LeRoy S. Palmer
H. Gideon Wells

OFFICERS AND COMMITTEES

Officers (July 1, 1944–June 30, 1945):

President, E. A. Doisy; *Vice-President*, A. B. Hastings; *Secretary*, A. K. Balls; *Treasurer*, W. C. Stadie; *Additional Members of the Council:* R. J. Anderson, H. T. Clarke, V. du Vigneaud.

Nominating Committee: H. B. Lewis (*Chairman*), W. M. Clark, C. F. Cori, H. A. Mattill, W. C. Rose, E. A. Evans, G. O. Burr, C. L. A. Schmidt, J. M. Luck.

Editorial Committee: (For the term 1939–45) P. A. Shaffer (*Chairman*), A. N. Richards, V. du Vigneaud; (for the term 1941–47) W. R. Bloor, H. A. Mattill, C. L. A. Schmidt; (for the term 1943–49) H. D. Dakin, J. M. Luck, D. W. Wilson.

ARNOLD KENT BALLS,
Secretary.

American Physiological Society

Symposium on the Cerebral Circulation

THE PRESENT STATUS OF KNOWLEDGE CONCERNING THE INTRINSIC CONTROL OF THE CEREBRAL CIRCULATION AND THE EFFECTS OF FUNCTIONAL DERANGEMENTS IN IT

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It is no longer a secret that in modern mechanized warfare man is definitely the limiting factor, for machines such as airplanes, tanks, other land vehicles, submarines, and surface ships are capable of performance which their human occupants cannot tolerate without loss of efficiency, health or life itself. One of the greatest challenges to physiologists in the present emergency lies in the identification and characterization of these physiological limitations as the necessary first step in devising means either for reducing the strains inflicted on the man or for increasing his ability to withstand them. Efforts along these lines have already achieved considerable success in relation to aviation, in which the strains are probably more numerous, varied and severe than in any other branch of military activity. According to pre-war publications (1) (22) the most important human strains of combat flying are related to anoxia, aeroembolism ("bends"), cold,

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acceleration, motion sickness, disturbances of the special sensory apparatus, fatigue and psychic deterioration. This list is not likely to require substantial modification when more recent experience is disclosed. Now it is a striking fact that the brain is the limiting factor with respect to all these strains, either because its functional capacity is reduced (as by anoxia, cold, or the cerebral anemia or congestion associated with acceleration), or because it is subjected to an intolerable bombardment by sensory nerve impulses (as in the pain of decompression sickness, the nausea of motion sickness, the discomfort of cold, or the accumulated psychic trauma associated with combat aviation). The blood supply of the brain then becomes a matter of immediate concern, not only because here, as elsewhere in the body, the capacity of the tissue to function is limited by the capacity of its circulation to meet its changing requirements, but for the additional special reason that the brain is unable to contract much of an oxygen debt and therefore is more subject than other tissues to derangement by an insufficient supply of blood. Two major questions then arise: What are the agencies by which the blood supply of the brain, or of its various parts, can be altered either to their advantage or disadvantage? and how would the functional capacity of these structures be affected if their blood supply is either deficient or excessive relative to their requirements?

These questions have been asked and answers to them sought for more than a century, and twenty years ago categorical answers to both of them would have been given without hesitation. The cerebral circulation then was held to be fitted passively to the needs of the brain by adjustments elsewhere in the body, and an intrinsic control over cerebral vessels was regarded as unimportant or non-existent (see (37) for the literature on this subject). The response of the brain to acute anemia was universally held to be stimulation followed by depression, ever since Kussmaul and Tenner (16) demonstrated that occlusion of the carotid and vertebral arteries causes violent generalized convulsions followed by paralysis and Rosenthal (21) showed that the respiratory and vasomotor centers likewise are strongly stimulated before they are paralyzed. With these seemingly unequivocal items of experimental evidence as a background, experimenters and clinicians came to hold the opinion that spasms of cerebral vessels, occurring spontaneously or elicited by suitable physical or chemical agencies, would elicit signs of cerebral stimulation and might be responsible for the convulsions produced by disease states or by drugs.

During the past twenty years, however, there has been a gradual accumulation of evidence against both of these older viewpoints. Studies of the cerebral circulation by a number of techniques have shown that the cerebral vessels possess considerable capacity for independent control in response to both nervous and chemical agencies; these observations are now so numerous (see (18) (19) (37)) that there is no longer any doubt about the necessity for revising the older idea that the cerebral circulation can be adjusted only passively. The discovery (13) and subsequent confirmation (see (28) (29) (30)), that the hyperpnea and hypertension of anoxemia, even the generalized convulsions elicited by cyanide (27), may be due to reflexes from the carotid and aortic bodies, in the absence of which anoxia is essentially depressant to the central nervous system, has cast doubt on the previously universal idea that acute cerebral anemia would necessarily produce strong stimulant manifestations. Yet while existing evidence justifies abandonment of the older viewpoints it is at present insufficient to permit the formulation of definitive new ones. Brief reasons for this statement will be presented below.

It is scarcely necessary to point out that progress in this as in any other branch of physiology depends on improvement over the methods previously used. In this particular case progress has been impeded by lack of realization of the special anatomical difficulties involved in studies of the cerebral circulation, which appears to indicate that these have not been sufficiently emphasized in the past. The next article has been compiled by an anatomist (Batson) who has been specially interested in this subject, in hopes of preventing a repetition of such wastes of time and energy as calculation of total cerebral blood flow in the rabbit from the volume measured in one internal carotid and the fraction of brain substance stained upon postmortem injection of dye into that vessel (15); or deductions as to the behavior of cerebral blood vessels from changes in blood flow through the internal carotid arteries of dogs (34) even though a few of the most direct communications with the external carotid system have been closed (3), since major communications certainly will still exist in cervical branches of the vertebral arteries, and probably in numerous other localities as well.

Next to a suitable animal preparation, the method used to evaluate the behavior of the cerebral circulation is the most important factor to be considered. In the third article of this symposium Gregg and Shipley, who have recently made a thorough comparative study of the various methods available for measuring blood flow elsewhere in the body (11), take up the methods that have been or might be used to obtain evidence bearing on the cerebral circulation and discuss the virtues and limitations of each.

The final article, by Cobb and Lennox, deals with the ideas now current in clinical circles as to the occurrence and consequences of functional abnormalities of the cerebral vasculature.

In all four parts of this symposium there is no attempt to present a complete review of the literature on the cerebral circulation, for this has been done elsewhere (18) (19) (37). My own contribution here will be limited to statements of impressions as to the present status of the two major questions noted above, with brief reasons.

1. *The intrinsic control of the cerebral circulation.* Most of the recent evidence bearing on this subject has been obtained from studies on cats, in which quantitative measurements of cerebral blood flow are practically impossible because of numerous and inaccessible communications between the intracranial and extracranial parts of the cephalic circulation. Realizing this, recent workers have made no attempt at direct measurements of blood flow but have resorted to detection of changes in flow by means of instruments applied directly to the brain. The first of these was a transparent window through which the pial circulation could be observed under the microscope (8) (37). The second was a thermocouple inserted directly into the brain tissue (25) (26) (31) (33). Both methods have the advantage of affording certainty as to the location of such changes as may occur, the disadvantage of being indirect and non quantitative with respect to actual blood flow changes. According to both methods the vessels in the parietal region of the cat's brain possess a vasoconstrictor innervation via the cervical sympathetic (26) (37), a vasodilator innervation through the great superficial petrosal nerve (4) (9), a capacity for being strongly dilated by many (28) (31) (37), weakly constricted by a few (31) (37) chemical agents. As a result of these findings it seemed proper to conclude (31) that the blood vessels in the brain do possess a well developed capacity for intrinsic control but that this differs from the control of blood vessels elsewhere in that it depends on tonic dilatation (rather than constriction) by means of chemical agents (rather than nerve impulses) of vessels having a high (rather than low) intrinsic tone, that intense constriction would result from diminution in this chemical vasodilator influence (not from vasomotor nerve impulses or chemical vasoconstrictor agents) and that the need for increased blood supply associated with increased functional activity would be met through dilatation of the finer blood vessels by the increased amount of vasodilator material being produced. Because excess CO_2 caused quite marked increase and diminished CO_2 a fairly marked decrease in the cat's cortical circulation, CO_2 was held to be the main if not the sole agent in the normal intrinsic regulation of the cerebral vasculature (28) (31).

This interpretation of the experimental findings seemed quite satisfactory until recently, when Dumke and I (6) finally succeeded in making quantitative measurements of total cerebral blood flow in monkeys. As far as I know, these are the only unequivocal quantitative measurements of cerebral blood flow that have ever been made under conditions approaching the normal. We were greatly surprised to find that cerebral blood flow was affected only slightly if at all by changes in CO_2 content of the inspired air, changes in the oxygen content showing more consistent and more marked effects—observations that have been confirmed in a series of similar experiments just concluded. We also were surprised to find that stimulation of the cervical sympathetic nerve had only negligible effects on the monkey's total cerebral blood flow. In other respects the results and interpretations were similar to those of the cat experiments: there were many agents by which cerebral blood vessels could be dilated but none at all by which they could be strongly constricted. Metrazol proved to be a very effective cerebral vasodilator. All these observations have recently been confirmed.

The lack of concordance with regard to the effects of CO_2 may be interpreted in one of two ways: either the response of the cortex (which was the only part of the brain studied in the cat experiments) is not representative of the great mass of brain substance, or else species differences exist. At present it seems probable that both may be true. When we applied a thermocouple to different parts of the cat's brain we found distinct differences in the response to cervical sympathetic stimulation, for while this caused consistent and quite marked vasoconstriction in the parietal region (26), it was less effective in the hypothalamic area (25) and ineffective in the medulla (33), pons (25) and occipital lobe (31). It is true that CO_2 produced vasodilatation in all these areas, but since the method was not quantitative we cannot draw any conclusions as to differences in the degree of this effect. No subcortical areas were investigated. Therefore we are at present without adequate information either as to the distribution or the degree of the dilatation of blood vessels produced by CO_2 in different parts of the brain of the cat, and we have no comparable information at all about the state of affairs in other animals except a few observations in the parietal area of the rabbit (31), where the responses were qualitatively similar to those obtained in cats.

As for species differences, decision must be reserved until the same method has been applied with equal success to different species of animals.

This has not yet been done. As just noted, we have used the thermocouple method in the parietal cortex of rabbits but in the similar attempts thus far made in monkeys the responses were less striking than in rabbits and much less striking than in cats. Whether this is due to faulty instrumentation or to an actual species difference has not yet been determined. The converse experiment—direct quantitative measurement of total cerebral blood-flow in animals other than monkeys—also has not yet been made. It will be impossible in the cat because of abundant and inaccessible communications between the extracranial and intracranial parts of the cephalic circulation (2). Measurements of flow through the internal carotid of the dog (34) are meaningless for the same reason; ligation of a few of the most direct channels connecting the internal and external carotid systems of the dog (3) (12) is still far from producing an isolated cerebral circulation because large, direct communications between the circle of Willis and the external carotid distribution still exist by way of free anastomoses between muscular branches of the vertebral and occipital arteries. In the rabbit these communications are much less well developed, and we have attempted to take advantage of this fact (31). We used a thermostromuhr to measure blood flow through the internal carotid, but were unable to secure satisfactory *in vivo* calibrations (which, in view of previous experience with the method applied to the renal circulation (35), we have come to regard as absolutely essential). It was in the course of attempts in that direction that we came to employ a crude bubble flow-meter, a refinement of which has been used for the monkey experiments (6). A critique of these and other methods will be found below in the article by Gregg and Shipley. Suffice it to say here that in our hands (as in those of others who have insisted on *in vivo* calibrations) the thermostromuhr has proved unreliable quantitatively and not entirely dependable even qualitatively, and we hold the burden of proof to be with those who claim that *in vitro* calibrations of a thermostromuhr are applicable to *in vivo* conditions.

It is impossible to say at present whether the above-mentioned differences between the monkey and the cat (the greater effectiveness of anoxia and the smaller effectiveness of CO_2 and of sympathetic nerve stimulation in the monkey) are due to differences in the responses of blood vessels in the cortex and in the deeper parts of the brain, or to species variations. At the present time, however, our faith in the supreme importance of CO_2 as a regulator of the cerebral circulation has been shaken because oxygen appears to be a more important agency than CO_2 in the monkey, and the monkey is at least anatomically closer to man than to the cat. This is a point of immediate practical importance in the interpretation of the effects of hyperventilation, the unconsciousness of which has been ascribed to intense constriction of cortical vessels because of diminution in arterial pCO_2 (28) (31). If the cerebral vessels of man are affected more by changes in pO_2 than in pCO_2, hyperventilation in the presence of anoxemia (as at high altitudes) should elicit much smaller effects than at normal ambient pO_2. There is nothing in the results thus far obtained in monkeys to justify the belief that hyperventilation can cause intense cerebral vasoconstriction, but the anesthetic may prevent such effects and further study is needed before a final statement is justified. At present I am inclined to attach greater significance to the monkey experiments than to any others, not only because these animals should resemble man more closely than cats, dogs or rabbits do, but also because they furnished us for the first time with actual quantitative measurements of cerebral blood flow. But then it appears that the recent trend of thought about the control of the cerebral circulation may have been unduly influenced by a situation peculiar to the cat.

If there are variations among different animals, and even among different parts of the brain of the same animal, it is obviously desirable to concentrate attention and effort on studies of the cerebral circulation in man. Apart from observations of the retinal circulation (which may or may not give valid information as to the behavior of the intracranial vessels and which certainly could not be made quantitative as to cerebral blood flow), direct inspection or thermocouple measurements in the human cortex (18) or internal jugular (10) (which likewise cannot be made quantitative), there are just two methods that have been used in the expectation of measuring cerebral blood flow in man. These are the occlusion plethysmographic procedure (7) and study of arteriovenous oxygen differences (14) (17) (37) (38). I believe the results obtained by either procedure to be untrustworthy because of factors that are inherent in the basic facts of the cerebral circulation and that therefore cannot be completely circumvented by refinements of technic. Reasons for this statement are as follows:

The plethysmographic technic has yielded figures of less than 250 cc. at rest and about 400 cc. maximum, for total cerebral blood flow in adult males (7). This would mean approximately 16 and 26 cc. per 100 grams per minute (assuming a brain weight of 1500 grams). The corresponding figures in our experiments on monkeys were about 60 and 110 cc. per 100 grams per minute (6). The discrepancy is further increased if the monkey figures are corrected for the reduction occurring on ligation of the basilar artery, which brings the mean

resting flow to about 85 cc. per 100 grams per minute.

It should however be pointed out that in a recent series of similar experiments the average resting cerebral blood flow (uncorrected) was only 47 cc. and a value equal to or greater than the mean of the earlier experiments was encountered only once in 30 animals The monkeys used recently were smaller and less resistant to the experimental procedures than those used previously. Furthermore, all the recent measurements were made while the animals were breathing oxygen, which in itself is likely to reduce cerebral blood flow in the monkey (6). We are uncertain, therefore, whether the earlier estimates were excessive or the recent ones deficient. In any case however, the figure given by Ferris (7) for resting cerebral blood flow in man is only a fraction of that corresponding with direct measurements of cerebral blood flow in the monkey.

This may of course mean either that the monkey figure is proportionately excessive for man, because of species differences or experimental artifacts, or that the plethysmographic method systematically undervalues the true flow in man. I prefer the latter explanation, because I know of no valid evidence in support of the former while good reasons exist for suspecting the latter (see below). Furthermore, in our recent experiments we collected samples of cerebral venous and arterial blood while measuring cerebral blood flow and thus were enabled to estimate cerebral oxygen consumption under different conditions. The highest value in the "normal" period was 4.5 cc. per 100 grams of brain (moist weight) per minute. This would mean 67.5 cc. for a 1500 gram human brain. At an A-V difference of 8 (20) the corresponding blood flow would be 840 cc., or 56 cc. per 100 grams, per minute, which is between the mean values of our two sets of experiments. At an A-V difference of 6.8 the blood flow would be about 1000 cc., or 67 cc. per 100 grams, per minute. If Ferris' values for blood flow are used, however, the cerebral oxygen consumption at an A-V difference of 8 would be 12.8 cc. resting and 20.8 cc. maximal, or 0.86 and 1.4 cc. per 100 cc. per minute. Cerebral O_2 uptakes as low as the latter were never encountered in our recent experiments in monkeys whose brains were functioning well as evidenced by active ocular reflexes or normal type of breathing, while figures as low as the former were met with only in moribund animals. Therefore, while species differences must always be suspected, it seems desirable at least to use these figures for orientation as to the magnitudes that may be involved and to examine the plethysmographic method for inherent sources of error.

The shortcomings of the occlusion plethysmographic technic are discussed in detail by Gregg and Shipley in the third article of this series. Suffice it to say here that the procedure contains two major sources of error, both tending to undervalue the actual flow and both as yet uncontrolled and unevaluated. One is inability of the spinal puncture needle to carry away the cerebrospinal fluid as rapidly as it is displaced by accumulation of blood in the cerebral veins. The other is escape of blood from the cerebral into the spinal venous system, and thence into the thoracic and lumbar veins, when the cerebral venous pressure is raised by jugular occlusion. The error introduced by the first of these, while not entirely negligible, is probably small compared with the second. Batson, in the next article of this series, points out the abundance of the communications among the cerebral, spinal, and systemic venous systems; as proof of the competence of these pathways to carry blood away from the head he cites cases of complete obliteration of the superior vena cava in man, without any symptoms of cerebral vascular impairment. We have frequently ligated the superior cavae of dogs and cats, and in our recent experiments on monkeys have routinely ligated both internal jugular veins as a necessary step toward the insertion of catheters into the jugular bulbs. Although careful watch was made for changes in respiration, circulation and ocular reflexes, no such changes were seen. Measurements of cerebral venous pressure, made in the course of some of our earlier experiments (23) during occlusion of the superior cava, showed a sharp initial rise to a plateau beyond which no further rise occurred no matter how long the occlusion lasted. That the pathway for cerebral venous return under such circumstances is the spinal sinus system is shown, not only by the anatomical data of Batson, but also by the fact that when the communications between the cerebral and spinal venous systems are ligated, jugular occlusion produces the characteristic picture of acute cerebral anemia (28, p. 655).

It seems certain that the occlusion plethysmographic technic cannot reveal the cerebral blood flow that existed before the jugulars were occluded, because the proportion of blood leaving the brain by way of the spinal sinus system must increase as cerebral venous pressure rises during jugular occlusion. Whether the method can properly be used for comparative purposes is debatable. It might be so used if the proportion of total cerebral blood flow passing from the cerebral into the spinal sinus system, and of that leaving the latter to enter the tributaries of the azygos and lumbar venous systems, were to remain constant in the face of probable alterations in the various pressures involved, viz. pressures in the cerebrospinal spaces, cerebral and spinal venous sinuses, superior caval (jugular and azygos) and

inferior caval (thoracic and lumbar) systems, as well as the intrathoracic and intraabdominal pressures. Constancy in the relationships among these factors would be difficult if not impossible to secure in living human subjects. The extent to which variations among them would modify the results will have to be ascertained by direct experimentation. In my opinion, this should be done before the method is further used or its results further accepted, even for comparative purposes.

The arteriovenous oxygen difference has been used by one set of workers to elucidate the metabolic activity of the brain on the assumption that cerebral blood flow remains unchanged, by another set to detect changes in blood flow through the brain on the assumption that cerebral metabolism is unaltered. Direct evidence bearing on this question has been obtained in our recent experiments (32) in which cerebral venous and arterial blood samples were collected while cerebral blood flow was measured, thus enabling us to obtain direct information about the correlations among cerebral A-V oxygen difference, cerebral blood flow, and cerebral metabolism. We found that changes in the A-V difference could be correlated reasonably well with either the blood flow or the metabolism in a given animal and within rather narrow limits, but neither correlation could be depended upon when the data were viewed as a whole. The only consistently valid correlation was that between cerebral metabolism and cerebral blood flow, for this seemed to hold good under all conditions compatible with functional activity in the brain.

The excellence of this correlation might mean either that cerebral blood flow in some way determines cerebral blood flow, or that an intrinsic mechanism exists whereby the blood supply of the brain is automatically adjusted to its metabolic requirements. We prefer the latter interpretation because, in some of our best-conducted experiments, we were able to alter the cerebral blood flow in either direction without corresponding change in cerebral metabolism or functional activity. But if this interpretation is accepted, it follows that the intrinsic cerebral vascular control, if it functioned perfectly, would completely prevent any change in the A-V oxygen difference even though the metabolic activity of the brain had changed considerably. Changes in the A-V difference would signify only that this mechanism was not completely successful, without of themselves giving any indication as to whether cerebral metabolism or cerebral blood flow was primarily involved.

Another fallacy in the cerebral A-V difference of O_2 (or anything else) is the irregularity in the communication among the cerebral sinuses. As Batson points out in the next article, the venous return from the entire cerebral cortex may pass through one internal jugular, that from the lateral ventricular and choroid plexus systems through the other. Samples of blood drawn from the two jugular bulbs might therefore differ considerably in chemical composition and deductions concerning metabolic events in the brain as a whole would be correspondingly invalidated.

Thus it appears that changes in the cerebral A-V oxygen difference cannot be interpreted either in terms of cerebral blood flow or cerebral metabolism. That the situation is more complex than it was thought to be is illustrated by the effects of CO_2 inhalation, which has been found to decrease the A-V oxygen difference in man (37). The conclusion that this proves the presence of a marked increase in cerebral blood flow must however be tempered by the fact that a similar decrease in cerebral A-V oxygen difference occurred during CO_2 inhalation in dogs whose cerebral blood flow was kept constant by means of a perfusion pump (23). The reason for this is unknown; reapportionment of blood among different parts of the brain was suggested (23) but a narcotic-like depression by CO_2 is equally possible.

The two methods that have been used for quantitative studies of the cerebral circulation in man therefore appear to be fraught with so many uncertainties that the results obtained by them are of limited value until some of the above-mentioned sources of error have been excluded, or at least evaluated. It is unfortunate indeed that now, when data concerning the behavior of the human cerebral circulation are urgently desired, the only thing that can be said is that a considerable amount of fundamental research will have to be done before such data become available. Yet in the past the first step toward real advances in clinical experimentation has often been dissatisfaction with the methods previously utilized, and it is to be hoped that history will repeat itself here.

The effect of drugs on the cerebral circulation is of considerable practical importance. Observations on total cerebral blood flow in monkeys (6) agreed with those previously made by less quantitative methods in cats and rabbits (31) (37) in indicating that there are many drugs by which the cerebral vessels can be dilated, none by which they can be strongly constricted. One important difference however was that epinephrine and its congeners (benzedrine, ephedrine) showed a distinctly greater tendency to constrict the cerebral vessels of the monkey than those of the cat or rabbit. Subsequent experience (32) has confirmed this impression, for in our recent experiments on monkeys epinephrine or benzedrine, given intravenously in dosage large enough to raise the blood pressure, caused less of an increase in cere-

bral blood flow than would be expected at the higher pressure. In no case, however, has there been a decrease in flow below the control level, and there is no reason to believe that these drugs could ever cause an actual spasm of cerebral blood vessels. The convulsant drugs metrazol and picrotoxin caused only an increase in cerebral blood flow at the time of convulsions, though a period of decrease below the control level typically occurred afterward. The only drug that we have found capable of producing a diminution in cerebral blood flow intense enough to be designated spasm is coramine; this effect was immediate but transitory and was associated with depression of circulation, respiration and ocular reflexes; recovery of all these functions then ensued and the convulsant effects of the drug became manifest together with an increase in flow above the control level. The significance of these relationships is at present obscure, but it is at least possible to say with confidence that the convulsant action of metrazol and picrotoxin is not due to intense constriction of cerebral blood vessels and the spasm produced by coramine is associated with depressant, not stimulant phenomena.

2. *The effect of acute cerebral anemia on cerebral functions.* At the outset it should be made clear that the ability of anoxia (however produced) to depress the activity of nerve cells (in the brain or elsewhere) is not now and is not likely ever to be called into question. The doubts which now exist have to do with the stimulant effects of anoxia of lesser intensity or duration than that which elicits depression. Reasons for the doubts are as follows:

First, reflexes from the carotid (and aortic) bodies are capable of accounting for some stimulant phenomena that in the past have been unhesitatingly attributed to direct anoxic stimulation of the central nervous system. This has been definitely proved with regard to the hyperpnea, hypertension and tachycardia of anoxemia (see (28) (29) (30)). The vomiting and convulsions of acute anoxemia may or may not be reflex in origin. Our attempts at settling this point were frustrated by inability to produce such effects in dogs, but intravenous injections of cyanide were found to elicit violent convulsions, associated with unconsciousness and followed by prostration and weakness, often by vomiting (27). These phenomena were either entirely abolished or greatly attenuated by denervation of the carotid and aortic bodies (27); the weaker stimulant effects sometimes observed after the denervation were associated with circulatory depression (in contrast with the stimulation seen in the intact animal) and may have been due to this (27). The convulsions, unconsciousness and other effects seen in the intact animal were not due to alkalosis consequent on the hyperpnea that preceded them because the pattern was not essentially altered when the animal was made to breathe 7% CO_2 throughout the entire observation period. There is little doubt therefore that the disturbance set up in the central nervous system by strong stimulation of the chemoreceptors can extend far beyond the respiratory, vasomotor and cardioregulatory centers.

Whether the convulsions of acute cerebral anemia (the "Kussmaul-Tenner spasms"), as well as the hyperpnea, hypertension, and changes in heart rate that occur when the carotid and vertebral arteries of a reactive animal are occluded, could also be referred to reflexes from the chemoreceptors, is at present uncertain though by no means improbable. It is true that occlusion of these vessels still caused some stimulation of respiration and circulation after denervation (24), but it is also true that the stimulant effects tended to be greatly reduced by the denervation in the small number of experiments so far performed. It is not at all unlikely that when the carotid and vertebral arteries are abruptly closed carotid pressure may fall so low as to reverse the flow of blood through the carotid bodies and permit venous blood to enter them (29), or there may simply be stasis and deoxygenation of blood in contact with the carotid body receptors (36). Thus the possibility of arousing strong reflexes under such circumstances is by no means fantastic, nor is their capability of then producing the familiar stimulant pattern, but the subject obviously needs further investigation.

The second type of evidence has been obtained from experiments in which total cerebral anemia is induced by rapidly elevating the cerebrospinal pressure to a level higher than the arterial. Many such observations have been made (see (37)) but as far as I know none have shown more than slight and transitory stimulation of respiration when the anemia approaches or reaches totality and in my own experience hyperpnea is the exception rather than the rule. There may be some movement of the limbs at the first injection of fluid, but this could be due to sensory impulses from the meninges rather than to direct involvement of motor neurones. In any case there is nothing resembling the violent dyspnea and convulsive movements associated with occlusion of the carotid and vertebral arteries.

The interpretation of these findings is not satisfactory without additional facts that are not available. The anoxia elicited by elevation of cerebrospinal pressure to a level higher than that in the aorta is total because all of the cerebral vessels must then be empty of blood (see (37)). One might assume that the neurones of the central nervous system are almost immediately inactivated under those circumstances and thus ex-

plain the absence of stimulant phenomena. But this cannot be true of the vasomotor center, the activity of which is progressively increased as cerebrospinal pressure rises (28) (37). Perhaps the latter are the only nerve cells to be stimulated by total cerebral anemia, but that conclusion is too important to be reached without further evidence. It is noteworthy that the period of anemic anoxia must have been preceded by one of stagnation because the first effect of the rise in extravascular (intracranial) pressure must have been to stop the flow of blood on the venous side, where the intravascular pressure is lowest. The onward flow then must stop while the vessels remain full of blood, and it may be for this reason that respiration persists until the rising cerebrospinal pressure is within a few millimeters of the arterial, or returns as soon as the former has fallen or the latter risen until they are nearly identical. It is improbable that the pressure in the capillaries in contact with the respiratory center is practically equal to that in the aorta when there is an onward flow through them, but these observations strongly suggest that the presence of blood in the capillaries supplying them is of the utmost importance to the ability of nerve cells to maintain their activity, even though there is little or no onward flow of the blood.

In view of these findings it is not possible at present to state categorically whether the effects of cerebral vasoconstriction would be stimulant or depressant to the activity of the part of the brain affected. The vasomotor theory of epilepsy has been abandoned (18) and if our results with metrazol and picrotoxin can be taken as representative convulsant agents cause an increase, not a decrease in cerebral blood flow. In monkeys in which cerebral angiospasm is present we find respiration gasping or absent and ocular reflexes abolished, and metrazol then fails to cause convulsions. All these findings obviously apply to the depressant stage of anoxia; they do not exclude a preliminary stimulation, but of the latter we have as yet seen no definite signs.

Pertinent observations in man have been made by inducing positive or negative acceleration. Positive acceleration causes cerebral anemia and leads to dimness of vision ("gray out") or temporary blindness ("black-out"), which may quickly be followed by loss of consciousness; recovery is prompt and there are no sequelae (1) (22). Negative acceleration causes cerebral congestion and manifests itself as red vision followed by blindness, mental confusion and even loss of consciousness ("red-out"); it is followed by severe, prolonged headache (1) (22). In neither case are convulsions or other stimulant effects a prominent feature before or during the period of loss of consciousness. As far as one can judge from these observations, neither acute anemia nor acute congestion of the brain of man characteristically causes stimulation before depression, but only depression which may perhaps be followed by stimulant phenomena.

These remarks should suffice to support the statement, made earlier in this article, that existing evidence bearing on the practical application of the physiology of the cerebral circulation is sufficient to prove the older, simpler viewpoints to be untenable in their original form, but insufficient to warrant the construction of definitive new ones. Reasons for the existence of this unhappy situation will be found in the two following articles dealing with the anatomical and instrumental difficulties involved in studies of the cerebral vessels. If, by placing these various aspects of the subject under a single heading and including a summary of current clinical viewpoints, others may be stimulated to fill in missing items of information, or to attack these problems with better prospects of success, we shall all feel amply repaid.

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ANATOMICAL PROBLEMS CONCERNED IN THE STUDY OF CEREBRAL BLOOD FLOW

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Organs with pedicles through which the major blood vessels enter and leave are most favorable for the study of blood flow. Next are those with a hilum in which the vessels are grouped. If the arterial side is used to measure the blood flow, the integrity of the stream must be maintained. On the venous side, it is permissible to measure the outflow directly by collection. This provides, at the same time, the data for determining the rate of flow and one of the required blood samples for studies of tissue metabolism. If the anatomy permits, the study of the venous outflow would seem preferable. Tubular organs, even if they possess a pedicle, have a complex vascular supply system. The brain, with its multiple vessels of entrance and exit, and neither hilum nor pedicle, retains the characteristics of its embryonic tubular origin. The anatomic relations are so complex and vary so much, between individuals as well as from species to species, that great care is necessary to obtain valid results. If the rate of flow is to be measured on the arterial side, an experimental animal is required in which it is possible to include all of the blood going into the brain and to exclude all going elsewhere. The anastomoses between arteries are so great that it is desirable to pick up the selected vessels as near to their entrance into the brain as possible, in order to lessen the possibility of disturbing anastomoses. The number, as well as the size, of anastomotic vessels is important.

A brief analysis of the features of interest in the well known blood supply of the brain in man will serve to clarify the problem, and at the same time serve as a starting point for considering the anatomic peculiarities encountered in available experimental animals.

In man, each of the paired common carotid arteries divides to form the internal and external carotids of its side. The internal carotids give off no branches before entering the skull. After entering the skull, but before joining the circle of Willis, there are a few minute branches, too small to be of significance, and the ophthalmic artery. The ophthalmic artery, in addition to supplying the strictly neural tissue of the orbit, is distributed to the lacrimal apparatus, the ocular muscles, and part of the nasal mucosa. In animals having a similar anatomy for the ophthalmic artery, this extracerebral circulation, while probably not of an amount to seriously disturb results, must be taken into consideration. The internal carotid arteries in man are the major source of arterial blood for the brain. Bilateral compression of the common carotids in the neck is followed in a few seconds by unconsciousness. One common carotid artery can be ligated in man, on occasion, without ill effect. The hemiplegias that have occurred following ligation may have been due to the anemia or, according to Dandy (1), to an embolus produced by the ligature. Dandy recommends a preliminary testing of the

effects of simple compression before operation, in order to evaluate the anatomic adequacy in the particular patient, and a slow ligation to prevent embolus formation and to develop collateral channels. The need for preliminary tests indicates the variations in human anatomy.

The paired vertebral arteries in man take origin from the subclavian arteries, and as they course up the neck, unlike the internal carotids, have numerous branches, the rami spinales, to the neighboring muscles. In man, these do not have great significance, but in some comparative forms with large neck muscles, these connections might be a major source of error. Once inside the skull, the vertebral arteries and their united continuation, the midline basilar artery, distribute numerous branches to the brain in the posterior fossa. The basilar artery resolves into the paired posterior cerebral arteries, which are a part of the circle of Willis.

While making injections, I have seen small arteries crossing the subdural space from the dura to the brain of man, particularly near the anterior end of the falx. Because of their small size and variability, they cannot be considered significant in the arterial supply of the brain.

Before leaving the arteries in man, the significance of the anastomoses between the two external carotid arteries must be outlined. These anastomoses are so rich that little discomfort is experienced after the ligation of a common carotid artery. Mont Reid (2) gives a complete discussion of this in his paper on arterio-venous fistulas. He shows that after ligation of a common carotid artery, its internal carotid, because of the anastomotic connections between the external carotids of the two sides, is fed through the external carotid artery. To occlude the internal carotid artery, Reid therefore ligated the common carotid and the external carotid. In an animal with similar relationship, a parallel procedure would permit the isolation of the internal carotid without disturbing the carotid sinus region.

In brief, in man the two large internal carotid arteries and the two small vertebral arteries enter the skull and supply the brain. They intercommunicate to a variable degree through the circle of Willis, and through anastomoses between arteries on the brain surface. The variation in size of these arteries and their communications determines the safety with which one internal carotid artery may be ligated.

In an animal similar to man, to study blood flow of the brain on the arterial side, the internal carotid arteries are the only vessels readily exposed. The vertebral arteries would have to be isolated or occluded after they attain the posterior cranial fossa. The ophthalmic arteries are the only significant arteries that leave the cranium for non-neural distribution.

The channels for the return of venous blood from the brain are very complex. An adequate concept of the problem is difficult without the study of corrosion specimens and other special injections. Because of the great number of cerebral veins that parallel each other, the low level of the venous pressure, the absence of valves, the direction of flow in many of these must be reversed frequently. The veins leave the brain and cross the subdural space to adjacent dural sinuses, into which they empty. Most of the veins from the cerebral cortex join the superior longitudinal sinus. However, several named anastomotic veins open into the transverse sinus near its sigmoid portion. The superior longitudinal sinus enlarges as it goes backward, and at the tentorium, with the two transverse sinuses and the straight and the occipital sinus, forms the torcular (winepress), or the confluence of the sinuses. Either name implies a misconception of function. "Occipital dural plexus" might better be applied, for only in a small number of cases do the vessels unite so that their contents flow together.

Three vessel patterns are recognized here: *1.* The superior longitudinal sinus continues as the left or right transverse sinus—usually the right. The straight sinus flows to the opposite side. Small channels effect an imperfect anastomosis. *2.* The superior longitudinal sinus divides and is distributed about equally to the right and left transverse sinuses. *3.* There is a true confluence of the several sinuses. Blood coming from straight sinus is from the veins of the lateral ventricles and the chorioid plexus, and might be quite different from that coming from the sagittal sinus which drains the cerebral cortex. In those cases in which there is no true confluence, the blood in the two internal jugular veins would differ correspondingly in its chemical composition.

Leaving the cranium, the jugular bulbs, because of their large size and direct continuation with the lateral dural sinus, have received most attention. There are many other venous pathways from the cranium, however, that do not join the internal jugular vein until a much lower level. The so-called sinuses on the skull base, such as the basilar, the cavernous, etc., are really plexiform networks which communicate with similar meshworks within the bones of the skull base, and the pterygoid plexus of either side, below the skull, and the veins of the orbit. Every nerve and arterial foramen in the skull base transmits some veins in this network.

From a corrosion preparation, one could describe this intracranial, extracranial, and intraosseus network as a single venous plexus in which the bodies of the sphenoid and the occipital bones

are embedded. These channels of outflow from the cranium, although individually small, are too numerous to be disregarded.

In the bones of the calvarium there are two sorts of veins; those veins which collect the metabolites from the bone itself, and those which act as by-passes between the dural sinuses and the extracranial circulation, or between different dural sinuses. Since there is free union between the vessels carrying the metabolites from the bone and those from the dural sinuses, there is a dilution of the venous return from the brain. The amount of blood from the bone can be estimated by noting the size of the several meningeal arteries, for the meningeal arteries are the nutrient arteries for the skull. In man, the anterior meningeal artery is a terminal twig from the internal carotid. It is too small to be of significance. The middle and posterior meningeal arteries are branches of the external carotid artery. The middle meningeal is the only one of these of large size. The veins in the skull vault communicate with the superficial venous circulation through emissary veins. The same name is used for those direct communications between the dural sinuses and the superficial veins. Ordinarily these emissary veins are not of a caliber to make them significant in quantitative studies of blood flow. However, occasionally one finds an entire sigmoid sinus draining out through a mastoid emissary vein. These mastoid emissaries are generally the largest, and subject to the most variations. In any animal species presenting the same vessels with a degree of variability comparable to man each individual would have to be studied, to find whether such channels were of a size to interfere with accurate quantitative work. The large diploetic channels mentioned above, sometimes called the diploetic veins of Breschet, enlarge with a chronic increase in intracranial pressure. The illustrations of the diploetic veins seen in the textbooks and atlases obviously do not represent the average condition. A radiographic survey of some sixty calvaria disclosed less than ten large enough to cast a distinct shadow on the x-ray film. In the human, therefore, this circulation in the calvarium raises two points of interest: the mixture of cerebral blood with cranial blood in the diploetic veins; and the several unpredictable communications of the cerebral circulation with the vessels of the scalp by way of the emissary veins.

This brings us to a most significant feature in the cerebral venous drainage—the network of veins which begin with the dural sinuses of the posterior cranial fossa, and extend the entire length of the spinal column. This plexus requires special methods of demonstration, and for that reason is not frequently studied. The best account and the best illustrations were provided by Breschet (3). This longitudinal plexus has been divided into several parts. I have reported (4) the ease with which flow takes place from end to end. The internal vertebral plexus occupies the space between the dura mater spinalis and the bone of the spinal canal. The external vertebral plexus surrounds the vertebral arches and lies in the deep back muscle. At least three pairs of longitudinal networks can be distinguished: the pair in front of the dura; a pair behind the spinal dura; and a pair on the side of the vertebral spine. Opposite the middle of the bodies of the vertebrae there is a large transverse connection between the longitudinal chains. Many smaller, irregular, connections unite all parts of this into a giant linear plexus. At each intervertebral space there are communications with the intracavity veins of the thorax and abdomen, with the intercostal veins, and with other veins in the body wall. In the neck there are numerous junctions with the veins of the neck viscera and those of the shoulder girdle. Other vessels go through each vertebra, also uniting the intracavity vessels with these spinal vessels. Since many of these veins are wholly surrounded by bone, we are not justified in considering them a blood lake, rather they are channels providing constant interchange of blood between the cerebro-spinal group of veins and the intracavity veins. This plexiform network is without valves, and many connections with the cavities are without functioning valves. The total cross-sectional area of this system as it leaves the cranium has not been estimated. From corrosion preparations it appears greater than the combined area of the two jugulars. This does not of necessity mean that the carrying capacity is greater. There exists considerable clinical evidence as to the capacity of this channel. In man, both internal jugular veins have been ligated, either simultaneously or within twelve hours of each other, a sufficient number of times without disaster to indicate that this vertebral plexus is sufficient to take over the entire drainage of blood from the cranial cavity (5) (6). This bilateral ligation has ordinarily been used only in cases of severe bilateral mastoid disease. If bilateral jugular ligation can be successfully practiced under these conditions, the plexus must be assumed to be one in constant use. Meltzer (5) reports that, in his case, there was no change in the eyegrounds after ligation of both jugular veins.

Another interesting series of cases presents more striking evidence of the adequacy of this set of channels. I have had the opportunity to study in some detail three cases of effort thrombosis involving vessels at the root of the neck. One case has been particularly informative because there is x-ray evidence of total occlusion of the superior vena cava and the vena azygos major. This has

been confirmed by surgical exploration. The x-ray studies with radio-opaque material show the altered course of flow. The total occlusion of the superior vena cava occurred three weeks after the initial injury. It is assumed that in three weeks the thrombus enlarged to a size at which this shut-off occurred. The patient's chief and only complaint was that his face was swollen. X-ray studies of the venous return, made by injecting, simultaneously, superficial veins in each arm, disclosed that the return flow was by the vertebral plexus of veins. At the first examinations there was no evidence of an increased return by way of the subcutaneous vessels of the thorax and abdomen. When it is realized that not only the blood from the brain, but the blood from the face and neck and both upper extremities, was forced to return over the vertebral plexus, and when it is realized that the mouth of the thoracic duct was occluded, the chief complaint seems trivial indeed. We must admit that the vertebral vein plexus would not be able to take over in this emergency if it were not already a definitely functioning system under normal conditions.

The sole complaint, in a second patient, was that his friends told him he was changing color; he was developing a reddish hue over his face and neck and hands. This first patient experienced dyspnoea on exertion and fatigue on slight use of the upper extremities. He would lose consciousness when in a horizontal position. Eighteen months after the acute onset, large veins appeared in the subcutaneous tissue on the thoraco-abdominal wall; the patient found that he could lie down without losing consciousness, and was now able to sleep in this position. We have here a set of channels of outflow from the skull which must be controlled if we are to measure blood flow on the venous side. The occipital sinus, either its straight or circular portion, the basillary sinus, the mastoid emissary veins, and the posterior condyloid veins, when present (about 60% of cases), all drain into this network.

To summarize the venous outflow from the brain in the human: blood may leave by the internal jugular veins by the forward anastomoses with the orbit and the pterygoid plexus of veins, by way of emissary vessels through the cranium, and especially important, by way of numerous channels which join the vertebral vein plexus. The significance of this plexus is that it appears to operate under normal physiologic conditions and in a certain number of individuals, at least, is capable of taking over the entire drainage after acute occlusion of the jugular veins.

The existence of a vertebral plexus of veins precludes the possibility of measuring cerebral blood flow on the venous side unless the plexus is closed. From its anatomic structure, it would not appear feasible to introduce cannulae for measuring flow. The detailed anatomy of the vascular system for most of the comparative animals has not been well worked out. This is particularly true of the veins. Therefore, I injected the cerebral veins in the Rhesus monkey, the rabbit, the dog, and the cat in a small series, and studied the distribution by radiographs. I can report that the vertebral vein plexus described for the human is at least as large in proportion in these four animals. Since this vertebral vein plexus is a survival of primitive embryonic channels, this similarity would be expected. There are indications of enough other channels to raise the question of whether the blood flow measurements should be made on the venous side even if the vertebral plexus is occluded. For example, Strauss (7) has pointed out a large emissary vein in the monkey which becomes superficial near the condyle of the mandible. I have confirmed the presence of this vessel in the radiographic films. The pterygoid plexus of the monkey, cat, dog, and rabbit, is also of a size comparable to that in a human.

On the arterial side, the question of the comparative anatomy has been discussed by Leonard Hill (8), and, more recently and extensively, by Ask-Upmark (9). Both of these accounts consider the collateral channels on the arterial side in a series of animals. For the anatomy of the arterial system of the dog, the description of Ellenberger and Baum (10) still seems the best. For the cat, a recent excellent account by Davis and Storey (11) clears up many moot points. It is sufficiently detailed so that all of the anastomotic peculiarities are adequately listed.

In addition to the internal carotids and the vertebral arteries which supply the brain in man, in other animals the external carotid and occipital arteries may function. The vagaries of the presence and absence of these four paired arteries and their intercommunications provide the major problem in studying blood flow on the arterial side. In addition, some animals have a peculiar elaboration of vessels known as a *rete mirabile*. This network provides intra- and extra-cranial junctions between the cerebral vessels and the external carotid arteries. Ask-Upmark believes that the *rete mirabile* is always associated with the participation of the external carotid artery in the cerebral circulation. Because of the extensive anastomoses between the brain vessels and the extracranial organs, it appears that any animal with a *rete mirable* is unsuited for measurements of cerebral blood flow from the arterial side. The manipulative procedures necessary to obliterate an anastomoses through a *rete mirabile* seem too great to be a laboratory routine.

The Rhesus monkey is without a *rete mirabile*

and, in the main, the arterial pattern resembles that of man. There may be a difference in the degree of anastomosis between the vertebral arteries and the vessels supplying the muscles of the neck. It has been possible in anatomic specimens of this monkey to inject the arterial mantle of the brain rather completely after ligation of both common carotid arteries and after the ligation of the basilar arteries of the base of the brain. These anastomoses were obviously on the surface of the brain itself, and are probably not significant when pressures are maintained on both sides of the ligature, as they would be in life. Although I have not tried this with a human brain, I think that the same would be true.

The Rhesus monkey would require the control of the internal carotids and the intracranial vertebral artery in order to study the blood flow. For practical purposes, the anatomy approximates that of man.

In the cat, the recent paper by Davis and Storey (11) has brought out a point imperfectly noted by earlier workers. The internal carotid, in their experience, does not have a lumen, hence it cannot be considered a competent vessel, as figured in the earlier diagrams. From the careful study of these workers, it is evident that the *rete mirabile* would be even more difficult to handle than assumed. X-ray films made of anatomic specimens of the cat after injection of roentgenopaque material, further emphasized the complexity of the region. The cat, therefore, is not suitable for the study of cerebral blood from the arterial side.

In the dog, the internal carotid joins with the external carotid by way of several fine branches to the middle meningeal inside of the skull. This is sometimes called a rete. The basilar artery is formed in a rather atypical manner from the vertebral and the occipital arteries. These several connections between the internal carotid on the one hand, and the external carotid and subclavian arteries on the other, make it difficult, if not impossible, to adapt the dog for quantitative flow studies under conditions approximating the normal.

In the rabbit, there is no *rete mirabile*. The brain is supplied by the internal carotid arteries and the vertebral arteries. The vertebral arteries are larger than the internal carotids. The rabbit should be a satisfactory animal in cerebral blood flow experiments, and has been used by Schmidt and Hendrix (12). The small size of the internal carotids is a drawback.

Of the animals reviewed, the venous side is unsuited in all for the study of the cerebral blood flow. This will probably be true for most if not all forms. The pattern of the veins, as with any low pressure system, is always complex. The use of the arterial side in an animal with a *rete mirabile* is undesirable, for the possibility of quantitatively controlling the anastomoses seems remote. Among the common animals, this leaves the monkey and the rabbit. In these, the vertebral arteries had best be eliminated in order to restrict anastomoses. Unfortunately, in the rabbit the vertebral arteries are larger than the internal carotid arteries. As for securing a proper sample of venous blood, the jugular bulb should be satisfactory—particularly if both sides are used. The region of confluence of the sinus should also be suitable. A too rapid aspiration might here withdraw blood from the vertebral vein plexus.

Among the animals, there may be one with internal carotid arteries and without a *rete mirabile*, and without vertebral arteries. All that could be asked for more would be that this animal have internal jugular veins that received no tributaries until far below the skull base. Studies of cerebral blood flow and of cerebral metabolism in vivo would then be comparatively simple. Up to the present time, no animal having these specifications has been brought to our attention.

A final word about estimating the brain area irrigated by a particular artery. Such estimations are generally made by injecting a color mass into the artery selected. The basis for the use of this method seems to rest upon the paper of Kramer (13). The total unreliability of the method, even when applied in the living animal, can be understood by referring to the argument that has gone on for decades as to the direction of flow in the fetal circulation. Using identical injection methods, workers have succeeded in obtaining evidence which proved opposing theories. Any one who makes injections of anatomic parts is familiar with the rules: use a thin mass or a solution of low viscosity for demonstrating the finer vessels and anastomoses; use a thick mass, large particles, and high viscosity to exclude them. So much depends upon the state of the tissue at the time of injection that one always expects to make several preparations and to select the best of the lot. A novice, by accident with luck, and one more experienced, by design, may inject the entire region or entire organ from a very minor vessel. In the injection of the monkey brain referred to earlier, the primary injection attempt was directed towards the spinal cord. The carotid arteries and the basilar artery had been ligated. The injection was made into the arch of the aorta to fill the segmental arteries of the cord. The carotid arteries had already received an injection with India ink. Much of the area stained with the India ink was colored over with the Cinnibar injection. Had the ligature been left off the carotid arteries, no doubt an injection of the entire carotid area could have been obtained. This experience must be considered

typical. I am inclined to feel that authors reporting similar areas of irrigation in a series of animals are only reporting the use of similar injection methods. As for the materials used for injections, it must be borne in mind that the color ground for artists passes through capillary beds quite as readily as water-soluble stains such as soluble Berlin blue. It is difficult to believe that in an organ like the brain, with rich anastomoses between arteries of visible size, one can obtain data sufficiently accurate for quantitative studies in physiology by anatomic injection.

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EXPERIMENTAL APPROACHES TO THE STUDY OF THE CEREBRAL CIRCULATION[1]

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The development of adequate methods and the overcoming of instrumental obstacles is an essential preliminary to the solution of problems dealing with the circulation. The object of this communication is to discuss the various devices and procedures that have been or could be used to study the cerebral circulation and to point out their respective merits and shortcomings. Such considerations should reveal the proper basis for the interpretation of the present and subsequent studies of the circulation of the brain.

CHANGES IN PIAL VESSELS. Changes in diameter of the pial vessels of anesthetized animals have been observed through a tightly closed skull window with the aid of binocular microscopes and photographs, the space between the glass and brain surface being filled with Ringer's solution (1, 2). The arteries in this group of vessels range down to a small size but include few if any arterioles. The changes in their external diameter, as observed under various conditions (drugs locally applied or injected, nerve stimulation, changes in blood pressure and chemistry) are undoubtedly correct. The extent to which these observations on the pial vessels apply to the unanesthetized state or the extent to which alterations in their bore may regulate flow through the brain substance has not been determined. From the limited fields of micrometric observation, investigators in general have exhibited a laudable restraint in drawing conclusions concerning any changes in vasomotor state existing in the blood vessels in other portions of the brain or in the arterioles and capillaries within the brain substance. Although it would be reasonable to expect that constriction of the pial vessels would be accompanied by a decreased blood flow and their dilatation by an increased blood flow, no evidence is available to indicate that the arterioles deeper in the brain substance do not exercise their own vasomotor control over the rate of blood flow independently of the larger pial vessels. Significant interpretations will be possible only when subsequent studies are able to reveal a positive correlation between rate of blood flow and size of pial vessels.

PERFUSION TECHNIQUE. A considerable amount of information has been gained from experimental preparations in which the brain is perfused with blood by a mechanical pump (3, 4). Such a preparation may be likened to that of the heart-lung

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or isolated heart as used for studies of the cardiac circulation. The main virtue of such perfusion technique is that the several variables can be controlled and the effect of any one may be determined separately. However, the oxygen consumption, A-V oxygen difference and blood flow, all so easily measured, are determined under such unphysiological conditions that the changes observed are of questionable significance and only with considerable reservations can they be said to apply to the normal intact cerebral circulation.

MEASUREMENT OF BLOOD FLOW WITH INSTRUMENTS REQUIRING SEVERING OF BLOOD VESSELS. The direct quantitative measurement of total cerebral arterial inflow requires the measurement of the blood flow in all arteries supplying the brain or the measurement of flow in one or more arteries, the remaining ones having been tied. Flow measurements made in only one artery (the others being left untied) may or may not indicate correctly the directional changes in total blood flow to the brain. Even if the remaining arteries are tied and total arterial inflow is then measured, the preparation becomes sufficiently removed from the normal as to limit the interpretation of results.

A number of instruments are available with which reliable measurements of blood flow may be made. In each case, the instrument must be inserted between the cut ends of a vessel. The venturimeter (3), Pitot tube and orifice meter (5) are basically the same in operation and record the pressure difference between two points in the flowing stream. The pressure difference, which is proportional to the flow, may be read from water or mercury manometers, or in the case of the Pitot tube or orifice meter, the recording device has a sufficiently high natural frequency as to permit optical recording of the rapid phasic fluctuations in velocity of blood flow (flow pattern). The rotameter (6) is a tapered vertical tube within which the height of a metal "float" varies with the rate of blood flow. This device is being extensively used to record mean flow in the coronary and peripheral circulation. More recently, a small special rotameter has been devised with an electrical unit for continuous optical recording of flow. Mean rate of flow may also be measured by timing the passage of an air bubble through a glass tube of known length and volume ("bubble meter," Dumke and Schmidt, [7]). Of these instruments, only the venturimeter and bubble meter have been used to quantitate cerebral flow.

All of these devices have advantages and disadvantages. As a group, they permit accurate measurement of blood flow. Some have individual technical advantages. For example, the rotameter and orifice meter permit continuous recording of flow changes. All limit flow to a variable extent and have the disadvantage of requiring their insertion into the severed vessel of an operated and anesthetized animal to which anti-coagulants have been given. These requirements must induce a variable and unknown degree of insult to the nervous, metabolic and cardiovascular system and therefore, the interpretation of the results in terms of the normal animal is necessarily limited.

MEASUREMENT OF BLOOD FLOW IN THE INTACT BLOOD VESSEL. These methods do not require severing of the blood vessel or the use of anti-coagulants and in most instances can be used in the unanesthetized state.

Thermostromuhrs. Changes in mean blood flow through vessels, including those supplying the brain, have been determined indirectly by recording the temperature difference of two thermal junctions applied to an unopened vessel when the vessel and blood between them are heated by means of high frequency current (Rein, 8) or direct current (Schmidt and Walker, 9, Baldes and Herrick, 10). Inasmuch as these three types of thermostromuhrs are subject to essentially the same errors, they will be considered together.

Schmidt and Hendrix (11) first suspected that this device (including their own) was subject to a number of possible sources of error, the collective effects of which could not be predicted, identified or controlled. Subsequently, extensive tests (12, 13) of the instrument (Baldes-Herrick type) made *in vivo*, and *in vitro* have indicated that the relationship of galvanometric deflection to rate of blood flow will vary with 1) the artery used and its degree of stretch, 2) the position and degree of angulation of the unit with respect to the artery, 3) the presence of periods of zero flow or back flow in the flow pattern of the metered fluid, 4) the composition of the immediate environment, 5) movements of extra- and intravascular fluid in the environment, and 6) viscosity of the metered fluid. Changes in the flow pattern are of particular importance. Many experiments have shown that when the actual intra-arterial mean rate of flow diminishes and short periods of back flow appear in the flow pattern, the thermostromuhr may indicate a very large increase in flow (12). The flow patterns of all arteries thus far recorded with the orifice meter either normally contained backflow, or it could be induced by the injection of drugs and other procedures (14). Since there is no assurance that the instrument will indicate correctly quantitative or even directional changes in flow, the use of the method is not recommended. Here, as with other methods, the use of a sound basic principle with the intent of detecting changes in *one* variable does not necessarily exclude "contamination" of the results by concomitant changes in other associated variables.

Electromagnetic flow meter. This method (15, 16) utilizes the principle that an EMF is induced in the blood stream as it flows through a magnetic field. While the apparatus is somewhat bulky, requires exteriorization of the vessel, and published flow patterns are damped (as compared with those recorded with the orifice meter), the method appears adequate for determination of mean rate of blood flow.

Needle thermoelectric blood flow recorder (Gibbs, 17). This instrument consists of a heated thermocouple (connected in series with a reference thermocouple and galvanometer) mounted in the end of a hypodermic needle and is inserted into an otherwise intact blood vessel. The galvanometric deflection varies with the rate at which blood flow "cools" the heated thermal junction. The instrument has been used to record changes in blood flow in the internal jugular vein of man. If 1, provisions are made for detecting changes in blood and body temperature; 2, the needle tip is known to be immobilized with respect to the vessel into which it is inserted; 3, the vessel diameter undergoes no significant change; 4, clots are not formed on the needle tip; 5, the velocity of blood flow over the needle tip remains proportional to the velocity of flow throughout the remaining cross section of the vessel, and 6, blood flow is at all times forward, then changes in galvanometric deflection should indicate correctly directional changes in flow. The extent to which such tests have been made in the individual experiments is not known.

MEASUREMENT OF "TISSUE BLOOD FLOW" WITH THERMOELECTRIC INSTRUMENTS. The Gibbs "needle" described above and its modification (Schmidt and Pearson, 18) have been used to indicate directional changes in blood flow in a localized area of tissue. The thermocouple (heated or cooled) is inserted a variable distance into the tissue and the temperature between this and another (reference) thermocouple recorded. An extensive evaluation of this method has been made by Schmidt and Hendrix (11). As applied to brain tissue, the method has the advantage of being simple in its application and operation, and also of permitting detection of changes in temperature within a localized area. The method has disadvantages in that 1, it is not specific for indicating changes in blood flow, since the temperature of the thermal junction may also vary with changes in heat production (metabolism); 2, it is not a quantitative method; 3, the tissue adjacent to the needle is not "normal" by virtue of the unavoidable trauma induced by insertion of the needle; 4, although the needle may be fixed with respect to the animal's head, slight recession or advancement of the brain on the needle tip due to changes in brain volume may easily simulate changes in blood flow. In most instances, it cannot be determined from the published work whether these potential sources of error have been circumvented by those using the method. Any attempt to make the method quantitative by subsequent calibration of the recorded temperature changes in terms of total blood flow through the tissue is unwarranted until it is established that the relationship of total blood flow to local temperature change remains constant during the time of an experiment and subsequent calibration.

CEREBRAL A-V OXYGEN DIFFERENCES VERSUS BRAIN CIRCULATION. The difference in oxygen content of the blood entering and leaving the brain depends on the rate of oxygen consumption of the brain and the rate of blood flow through it. This difference has been determined and used by some investigators to study the cerebral circulation.

The cerebral A-VO_2 difference has been used as an index of brain metabolism (19, 20). Changes in this figure have been noted in many circumstances in animals or humans in which each served as his own control or in which comparisons were made between groups of individuals. An increase in this value is taken to indicate that more oxygen has been diverted to the tissues (increased metabolism), a decrease that less oxygen has been used for cerebral oxidative purposes (decreased metabolism). This could be true only if the blood flow increased in the former instance, decreased in the latter instance or remained the same in both instances. However, there is no factual basis for this general assumption. On the contrary, extra-metabolic factors exist, such as blood pressure, blood gases and nerve action which may modify the A-VO_2 difference by inducing changes in the rate of blood flow. These are potent regulators of flow here and in other body regions and alterations in them are easily induced by changes in respiration and muscular activity. Hence, the blood flow must be known as to its magnitude and/or direction of change before the A-VO_2 difference can be used as an index of brain metabolism. If each animal or individual serves as his own control, a change in A-VO_2 difference indicates correctly the change in brain metabolism, except when A-VO_2 difference and blood flow are altered in opposite directions. In the latter case the change in A-VO_2 difference cannot be interpreted on a metabolic basis unless the absolute blood flows are known. If groups of animals or humans are to be compared, the A-VO_2 difference may be interpreted in terms of cerebral metabolism only if the absolute blood flows are known. (For this purpose, it is obvious that any instrument that records only directional flow changes is of no value.)

Actually, even if all extra metabolic factors which might regulate cerebral flow were eliminated, an increased A-VO_2 would not necessarily indicate increased metabolism. An increased metabolism (tending to increase A-VO_2 difference) is associated with an increased elaboration of metabolites and the latter, particularly CO_2, which is known to dilate the vascular bed, thereby increases the rate of blood flow and tends to decrease the A-VO_2 difference. Hence, an increased A-VO_2 difference will indicate an increased metabolism only if it can be demonstrated that the vasomotor response (dilation with increased blood flow) does not overcompensate the oxygen utilization in its effect on the A-VO_2 difference.

The evaluation of changes in brain metabolism from measurements of arterial oxygen saturation must be placed in the same category. Although an observed decrease in oxygen saturation signifies a decreased amount of available oxygen per unit volume of blood, the rate of blood flow and venous oxygen saturation must also be known before the oxygen utilization (or metabolism) may be said to have decreased.

The difference in A-VO_2 has also been used as an index of changes in cerebral blood flow. According to the interpretation of some investigators (21, 22) changes in total cerebral flow are largely directed toward a maintenance of a constant CO_2 tension and pH of the brain cells and are not adjustments to the nutritional requirements of the cells. The metabolic rate of the brain is thus regarded as being essentially constant and any significant change in A-VO_2 difference is the result of a change in cerebral blood flow (an increased A-VO_2 difference indicating vasoconstriction and reduced flow, a decreased A-VO_2 difference indicating dilatation and an increased flow). This view has apparently arisen from the experimental demonstration that alterations in arterial content of CO_2 and O_2 alter cerebral flow so that changes in the vasomotor state are indicated (23). There is no more justification for this generalization than for the opposite view that changes in A-VO_2 difference reflect only changes in brain metabolism. Changes in blood flow and in A-VO_2 difference must be measured simultaneously and in each circumstance before change in the latter can be interpreted.

It is our opinion that the use of A-VO_2 difference as an index of brain metabolism or of change in cerebral flow has resulted in the accumulation of a large amount of data which can be permitted only a limited interpretation, except in those few instances in which the significance of alterations in A-VO_2 difference has actually been determined by also measuring the blood flow. One must therefore regard many of the experimental results as being an end in themselves since the interpretations accorded them will not have a basis in fact until adequate tests are available to validate what are now unwarranted assumptions.

"PLETHYSMOGRAPHIC" METHOD. Recently, Ferris (24) has advanced a method for the "objective measurement of a function of total intracranial blood flow in man". The rate of displacement of cerebrospinal fluid (CSF) through a large bore needle inserted into the lumbar subarachnoid space is measured when a special cuff about the subject's neck is inflated to 60–80 mm. Hg. The bony craniovertebral covering is said to serve as a rigid enclosure within which the distention of the cerebral veins (incident to the inflation of the neck cuff) causes a comparable displacement of CSF through the lumbar needle. Hence, it was concluded that "if the CSF is allowed to flow out of the subarachnoid space during a period when venous outflow from the cranium has been halted, then the rate of CSF flow should represent the rate of arterial inflow to the cranium". Certain assumptions must be examined upon which the validity of this indirect method depends.

Two of the more important assumptions, that 1, the craniovertebral cavity is a rigid container, and 2, venous outflow from the cranium is halted by this procedure, will be briefly considered. The cranial and vertebral bony covering (of the adult) is sufficiently indistensible to be considered rigid, thereby permitting the more general application of the Monroe-Kellie Doctrine. However, there are many distensible and compressible epidural spinal veins (cf. fig. 1). Hence the CSF displaced by venous distention in the cranium may not all be recovered from the spinal needle, since a variable portion may displace, by compression, an equivalent amount of blood from the epidural veins. One must therefore regard the natural craniovertebral "plethysmograph" as being not a rigid container but rather a somewhat distensible sac within a rigid container.

Is the venous outflow from the cranium halted with cuff pressures of 60–80 mm. Hg? Ferris states that "leakage of intracranial blood past the cuff being assumed to be negligible, the forward flow of intracranial venous blood can be said to stop during the period of CSF displacement". This assumption (without published experimental verification) constitutes the most important basis for the validity of the method. There are reasons to believe that although the venous jugular flow beneath the pressure cuff may be temporarily halted, the venous outflow from the cranium is never stopped under these conditions. From the anatomical standpoint, the spinal veins which communicate superiorly with the basilar plexus and occipital sinuses, and inferiorly with the extravertebral veins, constitute a potentially large and variable pathway for a drainage of

venous blood from the cranium. In addition, the internal jugular veins near their exit from the cranium communicate with the very sizeable common facial veins, anastomosing branches of the external jugular veins, a variable number of pharyngeal veins and, lower down, the superior thyroid veins. It is exceedingly unlikely that a pressure cuff of any design could be applied to the neck so as to completely occlude all of these communications. Hence it is highly probable that after inflation of the neck cuff intracranial venous pressure rises abruptly, but blood continues to leave the cranium, not only by way of the spinal veins, but also via the internal jugulars to progressively fill the much more distensible extracranial veins with which the internal jugulars communicate (cf. diagram). These unblocked intracranial and extracranial circuits function as two "plethysmographs" connected in parallel; the one has a fairly rigid covering and a sizeable "leak", the other a distensible covering. A given increment of intracranial venous blood will preferentially take such paths of low resistance rather than that of high resistance (intracranial venous distention with displacement of CSF against a considerable resistance head). Since the intracranial venous pressure is the common driving force in all instances, the rate of CSF displacement, the rate of outflow through the spinal veins and the rate of extracranial venous filling will vary inversely as their respective resistance heads. With so many avenues of escape for venous blood, even a complete occlusion of compressible veins in the neck can be considered "effective" only in the sense that it retards (by an unknown and undoubtedly variable amount) venous outflow from the cranium. Obviously, unless the resistance heads of 1, [spinal vein outflow, extracranial venous filling, venous escape beneath the pressure cuff] and 2, [CSF outflow] retain a constant relationship to each other, the measured rate of CSF outflow will bear no constant relationship to the rate of intracranial arterial inflow. There are a number of factors which may affect this relationship. Subjects will vary with respect to the size, potential volume and anatomical placement of the various extracranial veins emptying into the internal jugular vein. Even in the same subject, the degree of constriction and number of veins constricted may vary with the placement of the cuff about the neck. There is no reason to believe that the cervical veins, including the spinal veins which are anatomically protected from cuff compression, have similar carrying capacities among different individuals. The resistance head to CSF displacement may vary with the effective diameter, length and other unknown resistance factors concerned with the intraspinal conduction of CSF. Hence, although the rate of CSF displacement may be considered "a function of the rate of total intracranial blood flow", there is as yet no reason to believe that it is necessarily even an approximately constant function of total arterial inflow.

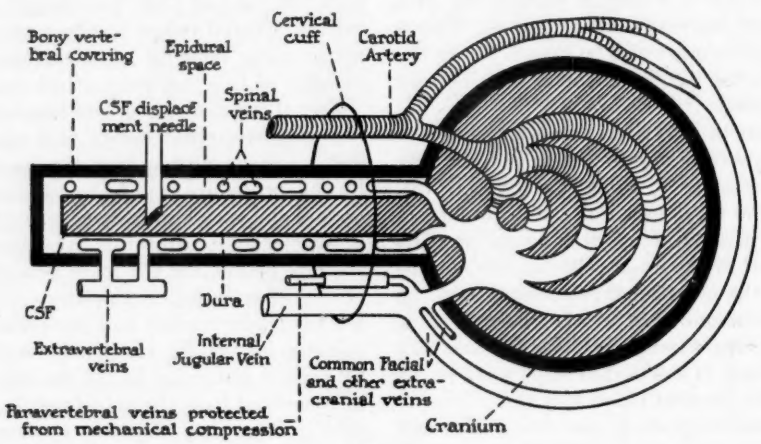

Fig. 1

Even if the aforementioned assumptions were valid, additional objections invalidate the assumption that a fixed relationship between CSF outflow and cerebral arterial inflow has been established. These have to do with the 1, resistance head to CSF displacement; 2, the distensibility of the intracranial vessels, and 3, the effect of the cervical cuff upon arterial flow to the brain.

In the measurement of cerebral blood flow by the so-called "natural plethysmograph" the CSF is displaced from the cranium and must traverse or progressively displace fluid through the subarachnoid space of the spinal canal, lumbar needle, and a portion of the recording apparatus. The resistance of the lumbar displacement needle has been measured with respect to the rate of CSF

outflow (24) but the total frictional fluid resistance between the cranium and the recording apparatus has not been determined. Inasmuch as the CSF pressure is recorded from a needle only 1 or 2 intervertebral spaces away from the lumbar displacement needle, the pressure recorded during CSF displacement represents the friction head of only a short section of the spinal canal, displacement needle, etc. It is not unlikely that the total frictional head opposing the free displacement of CSF from the cranium may be of considerable magnitude and may vary significantly from subject to subject.

The fact that CSF is displaced with venous compression in the neck must mean that the intracranial blood vessels (predominantly the veins) become distended. The distensibility of these structures is a matter of considerable importance. The veins within the cranium are supported in such a manner that they do not normally collapse or passively relax to any great extent. Hence, in the control state, the intracranial veins are already of such diameter that a small increment of venous blood may distend them to their free limit. Ferris has demonstrated that in subjects with normally low CSF pressures, or in those whose pressures are artificially reduced (by withdrawing CSF), the CSF displacement rate and pressure response are less than those observed with subjects whose CSF pressure is normally higher or is artificially elevated. He suggests that, owing to the relatively low CSF pressure in those cases, the intracranial veins are initially distended and are incapable of appreciable further distention. In order to be certain that the veins are in a state of partial collapse during the application of the method, routine adjustment of the CSF pressure to 180–200 mm. H_2O (by addition of Ringer's solution) is said to eliminate the poor flow and pressure responses. However, in 45 subjects with the lumbar displacement needle closed, compression of the neck veins with 544 mm. H_2O pressure caused the CSF pressure to rise to only 500 mm. H_2O or less (variation 225–560) in 29 subjects (64%). This would indicate 1, a rather variable and in many instances poor transmission of intracranial venous pressure to the surrounding CSF even though the latter is still confined within the cranial cavity, or 2, the intracranial venous pressures does not consistently become elevated to the pressure level of the compression cuff (significant leaks by way of uncompressed veins?), or 3, loss of pressure and CSF by displacement of blood in the epidural spinal veins. Hence, one cannot be certain *a*, that the intracranial vessels have sufficient passive distensibility to be able to displace CSF at a rate equal to the arterial inflow over a period of 5–10 seconds, or *b*, that a variable amount of CSF will not be "lost" in compression of the spinal veins, or *c*, that the frictional resistance encountered in transit within the spinal subarachnoid space does not significantly limit the rate of CSF displacement.

Ferris (24) states "That the application of external pressure to an artery does not affect the flow through it until the former exceeds the internal pressure is a well-known hydrodynamic fact." Our concept of events is somewhat different. An artery will undergo changes in diameter with changes in distending pressure. It can easily be demonstrated that if an artery is distended by a mean pressure of 100 mm. Hg and is subjected to an external pressure of 80 mm. Hg, the artery will acquire a diameter equal to that of an uncompressed artery having only a distending pressure of 20 mm. Hg. It must follow that, according to Poiseuille's law, the viscous retardation of flow will be increased and blood flow will be decreased. Hence, limitation of arterial blood flow to the brain by inflation of the neck cuff cannot be assumed to be negligible until actual measurements are made. The "effective arterial pressure head" must also be considered. Before the cuff is inflated, the effective arterial pressure head is equal to the systemic arterial pressure minus systemic venous pressure. Inflation of the cuff will ultimately (time of occurrence not known) decrease the effective pressure to a value equal to systemic arterial pressure minus the cuff pressure of 60–80 mm. Hg. It is not improbable that arterial inflow to the cranium is thereby significantly and rapidly reduced. The immediate flow retarding effect of venous back pressure is evident even in the plethysmographic recording of blood flow to a limb in which instance, the veins are comparatively free to distend and venous pressure to rise more slowly (25).

Thus far, the validity of the flow method has been examined with respect to the justification of various assumptions attendant to the method. For the present, many of the assumptions must be considered unjustified. The method may also be examined on an empirical basis, i.e., do the results with this method agree with those found by other methods?

Although the proponents of this method hold the belief that the inherent errors are slight, the average rates of CSF displacement (125–150 cc./min.) are thought to represent "actual rates of intracranial blood flow not in excess of 250–400 cc./min.". The reason for the correction factor is not given. If the latter figures are accepted as the normal flow range, the blood flow to an average 1500 gm. brain would be only 0.167–0.267 cc./min., figures which contrast markedly with 0.85 cc./gm./min. found for the monkey by Dumke and Schmidt (7). Until the actual intracranial blood flow can be determined simultaneously by an

adequate method, the rate of CSF outflow cannot be considered to have any proportionate constant relationship to the undisturbed intracranial flow which exists prior to the creation of abnormal pressure gradients necessary for the operation of the method.

Regardless of the magnitude of error in the quantitative use of the method, changes in the rate of CSF outflow are reported to indicate the same directional change in intracranial flow as those observed with the use of other methods. Both with the thermoelectric method of Gibbs and this method hyperventilation and CO_2 inhalation cause a decrease and an increase respectively in cerebral blood flow. Ferris (24) observed that elevating CSF pressure from a value of 200 to 350 mm. H_2O decreased the rate of CSF displacement 35–40%. However, Wolff and Blumgart (26) present evidence that, in cats, elevation of CSF pressure to 748 mm. H_2O causes little if any decrease in intracranial *velocity* of blood flow and further suggest that compensatory dilatation of the intracranial vessels probably makes even less likely any significant decrease in minute volume flow. It is not unlikely that elevation of the CSF reservoir in the method used by Ferris merely adds that much more hydrostatic pressure to the resistance head against which CSF is displaced, thereby decreasing the rate of outflow.

The cranivertebral plethysmographic method of Ferris is an ingenious approach to the difficult problem of determining total intracranial blood flow. In spite of its advantages as an indirect method, it also requires, in common with all other indirect methods, the necessary proof of its ability to indicate correctly the actual occurrences. Until more experimental tests and data reveal the operative mechanism of the method, the interpretation of results cannot be considered to have a sound hydrodynamic basis.

SUMMARY. A limited number of representative methods and devices, available for determining blood flow, have been discussed above. With the exception of perfusion experiments, all of the procedures have involved making observations from which the magnitude of, or directional changes in blood flow are determined only indirectly. In order that any direct method be considered valid, it is necessary that *1*, the available quantity actually measured varies in constant relationship to the unavailable and unknown quantity being measured indirectly; *2*, other variables which change spontaneously or are induced by the procedure do not modify this relationship. Since most indirect methods are used without exhaustive verification that these requirements are met, it becomes necessary that the investigator make several assumptions, some of which have been stated, others implied. Unless *all* of the assumptions are based upon tested and uniformly accepted relationships, the results and conclusions drawn will be open to question. The significance of any interpretation will therefore vary with the number and validity of the assumptions required in the application of any indirect method. In instances, unwarranted assumptions have been made in spite of adequate available tests to determine their validity.

It is obvious that without thorough knowledge of the principles and mechanisms by which any method operates, one cannot accept it as being theoretically adequate under any condition. A method or procedure too often acquires the unearned stamp of "validity" merely because the early results were shown to be the same as those obtained by other tested or untested methods. It is hoped that future tests and experiments will establish both physically and physiologically sound bases for many of the present indirect methods so that the results obtained may be accorded equally sound interpretations.

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CEREBRAL CIRCULATION—INTRINSIC CONTROL AND CLINICAL PHENOMENA

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In the organism of man there are two main integrating mechanisms: The blood stream and the nervous system; together they reach every living organ. Between these two integrators there is a reciprocal relation: the nervous system is dependent for its life upon the blood supply and the maintenance of blood supply depends upon a normally functioning central nervous system, which has vasomotor control represented at various levels, e.g., cortex, hypothalamus, hindbrain and spinal cord.

The control of cerebral circulation can be divided into extrinsic (extracerebral) and intrinsic (cerebral). The extrinsic factors are the reflex arcs from special receptors that work through the hind-brain nuclei. First there is the carotid reflex zone containing receptors through which chemical and pressure stimuli are transmitted over the glossopharyngeal nerve to centres in the hindbrain. As Weiss expressed it, the carotid sinus "is placed at the point of entrance of the arterial column into the brain, a vital organ most sensitive to fluctuations in the circulation, in order to maintain a constant supply at an optimal pressure." Other pressure-sensitive receptors are located in the aortic arch, in the heart, and in pulmonary artery, vena cava and splenic artery; these send impulses to the medulla oblongata to control reflexly circulation via the vagus nerve or spinal cord and spinal nerves. Last, and perhaps most important of all, is the effect of the carbon dioxide and oxygen content of the blood upon the vasodilator and vasoconstrictor centres in the hindbrain. The function of all these reflex arcs is to maintain not only an adequate and relatively constant blood supply to the brain, but one which contains the necessary chemical constituents. Other important extrinsic factors are the resistance of the arterioles throughout the body, the amount of venous blood returned to the heart and the condition of the heart muscle. In fact systemic arterial pressure is by far the most important single item in controlling cerebral blood flow.

Intrinsic or cerebral control. Although passive changes in the size of the cerebral vessels are often caused by changes in systemic blood pressure, changes in caliber due to change in muscular tension of the arterial walls may overcome moderate or gradual fluctuations in pressure. Such changes must be due to muscular activity. When active changes occur, one usually finds arterial constriction following a rise in blood pressure and dilatation following a fall.

Active changes in caliber may result from a number of stimuli. The simplest is perhaps direct trauma to the walls of the vessels. This has been seen by Florey (1) and others, and is always pathological.

Changes in the chemical composition of arterial blood cause important alterations of cerebral blood flow. In animals observations have been by means of windows placed in the skull, flow recorders placed in the brain and perfusion experiments. In man, evidence has been gathered from inspection of retinal vessels, measurement of spinal fluid pressure, including the plethysmograph method of Ferris, a thermoelectric flow recorder place in an internal jugular vein, and measurements of cerebral arteriovenous oxygen differences. Authors using different material and procedures agree with the observations of Wolff and Lennox (2), and Lennox and Gibbs (3) that increase in arterial carbon dioxide causes profound dilatation of cerebral arterioles with increase in the speed and volume of cerebral blood flow. Reduction of arterial CO_2 has the opposite effect. What is most significant, the effects are specific for cerebral vessels, the circulation of the extremities tending to decrease as that of the cerebrum increases. Alterations of pH produce effects that

parallel those of CO_2 tension. The relative significance of these two constituents has not been determined. The effect of changes of arterial oxygen are relatively mild and in the opposite direction to changes induced by carbon dioxide. Anoxemia causes some dilation of cerebral vessels and increase of blood flow in spite of the cerebral vasoconstricting effect of the loss of CO_2 due to the accompanying hyperpnea. Breathing of oxygen causes mild vasoconstriction. With severe anoxemia the addition of carbon dioxide to the inhaled mixture improves cerebral blood flow and postpones loss of consciousness. Alterations of arterial glucose do not greatly effect the cerebral circulation unless hypoglycemia is profound enough to impair cerebral function as shown by loss of consciousness. During the coma of insulin shock, the reported decrease in the A-V oxygen difference is possibly a result of increased blood flow although this point has not been adequately studied by actual blood flow measurements.

"Total" arrest of cerebral blood flow has been maintained in man for one hundred seconds without ill effect (4). Asphyxia of the tissues of the vessel wall due to slow blood flow (termed by Van Slyke "stagnant anoxia") is an important mechanism causing dilatation. This condition in the brain may result from general or local causes, viz. anything that causes low arterial pressure or high intracranial and venous pressure. Partial compensation for the slowing of blood flow is thus established. The dilatation is probably due to an asphyxial effect on the arterial walls, not to a nerve reflex, for it is unaffected by cocaine or by atropine applied locally to the vessels. If the vasodilatation is due to a fall in arterial pressure, it will be seen that when the blood pressure rises again, the relaxed walls dilate still further for a few seconds; then (while the pressure is still rising) constriction steadily takes place as the asphyxial condition is relieved by the improved flow.

Vasoconstriction due to innervation. It was long believed that there was no innervation of the cerebral arteries by sympathetic vasoconstrictor nerves. This belief was generally held, in spite of some early observations by Wiggers (5) and others, until Forbes (6) and his co-workers conclusively proved the presence of vasomotor nerves in 1928. This was done by use of a cranial window and microscope. The changing diameters of vessels in the pia-arachnoid over the parietal cortex were observed and recorded. For this work they used mostly cats, a few dogs and several monkeys. Their findings may be summarized as follows:

In more than 300 animals stimulation of the cervical sympathetic nerve has resulted consistently in constriction of arteries in the pia. The sympathetic fibers responsible for the reaction were found to pass through the middle ear in close association with the carotico-tympanic nerves which serve as pathways for the sympathetic impulses that dilate the pupils. Sympathetic nerve fibers via the stellate ganglion and vertebral nerves exercise no influence on pial arteries of the parietal region.

Forbes (7) says that: "The chief characteristics of this arterial constriction are as follows:

"1. It is strictly ipsilateral, that is, the vasoconstriction occurs only on the same side of the head as the nerve stimulated. No exceptions to this rule have been observed.

"2. It appears to be independent of changes in systemic arterial pressure, since it takes place when the latter is rising, is falling, or is constant.

"3. It occurs even when the greater part of the extracranial circulation is eliminated by clamping one or both external carotid arteries.

"4. It occurs in the completely isolated head, perfused through the carotid arteries of another animal. This fact as well as its unilateral character show definitely that humoral substances are not responsible for the reaction.

"5. It is abolished by the previous application of cocaine, novocaine, or ergotamine locally to the pial arteries under observation. Such procedures would be expected to inactivate nerve elements in the walls of these vessels. The action of ergotamine confirms the fact that the nerves involved are of sympathetic origin.

"6. It has been observed consistently only with arteries larger than 50 microns in diameter. With the smaller arterioles and capillaries no consistent change in caliber has been seen. It is interesting that Penfield found histological evidence of nerve fibers only on arteries above this size.

"7. The amount of constriction is small—an average narrowing of only eight per cent has been observed.

"8. Compared with the vasoconstriction observed in other organs, that in the brain is slight. When the cervical sympathetic nerve is stimulated, arteries in the skin constrict ten times as much as those in the pia and in the dura the arteries constrict almost eight times as much."

When the cervical sympathetic trunk was cut and the superior cervical ganglion removed, Forbes saw no subsequent dilatation of the pial arteries that he was watching under the window. But early experiments of Talbott, Wolff and Cobb (8) showed that capillary counts were greater in vitally injected brains, i.e. more capillaries received the injected fluid, in the hemisphere on whose side the sympathetic nerve was cut than in the opposite normal control side.

When cocaine is injected intravenously there is no evidence of increased sensitivity of the sympathetic vasoconstrictor reaction in the pia, such

as Rosenblueth and Cannon have found elsewhere. No increased sensitivity of the arteries follows denervation. When the superior cervical and stellate ganglia are removed and suitable time is allowed for degeneration of the nerve endings, adrenalin applied locally to the pial arteries causes no greater constriction than it does in the normal animal.

The venules in the pia constrict as much as or more than the small arteries when adrenalin is applied locally. Moreover, the venules sometimes constrict in response to stimulation of the cervical sympathetic nerve.

Schmidt using a thermoelectric flow recorder obtained evidence of retarded flow on stimulation of the cervical sympathetic nerve. This effect was noticeable chiefly in the parietal cortex, less in the hypothalamus and practically not at all in the medulla. The change in flow appeared to be independent of changes in blood pressure, but the extracranial circulation was not excluded in his experiments. Bouckaert and Jourdan (9), using three different methods, attempted to eliminate the extracranial circulation by a radical operation, and perfused the isolated head. On stimulation of the cervical sympathetic nerve they obtained evidence of vascular constriction and a reduced flow through the tissues receiving the blood, but it is by no means certain that the brain was solely or predominantly concerned (see the preceding articles by Schmidt and by Batson). Many investigators using perfusion experiments have obtained similar results.

Vasodilatation due to parasympathetic innervation. Evidence of a vasodilator innervation was first obtained in a joint experiment with Penfield conducted in Cobb's laboratory (7). On a sympathectomized monkey it was shown that stimulation of the facial nerve near the medulla oblongata caused dilatation of pial arteries in the parietal cortex. This reaction occurred only on the same side of the head as the nerve stimulated. Later work corroborated this and added new facts. Chorobski and Penfield showed that nerve fibers pass from the facial nerve through the geniculate ganglion and the great superficial petrosal nerve to the carotid nerve ascending the internal carotid artery. Experiments proved that stimulation of the facial nerve at the geniculate ganglion causes prompt dilatation of the arteries in the pia of the parietal region. This reaction is always ipsilateral in location.

Vasodilatation is significant only if it occurs when the blood pressure is normal at the beginning and remains nearly constant throughout the period of stimulation. This is important because it has been found that if the systemic arterial pressure falls below a certain critical level the pial arteries always dilate as a consequence of the retarded blood flow. Local applications of cocaine and of atropine abolish the neurogenic dilatation, though they have no effect on the dilatation due to low blood pressure. Ergotamine (locally) does not affect the reactions.

In regard to the functional importance of the cerebral vasomotor mechanism the evidence at hand warrants only a few suggestions. Since it is more effective in some parts of the brain than in others it may aid in diverting the blood from one region to another; it may help arteries to regain their normal caliber, as after extreme dilatation, and it may limit undesirable fluctuations and thus aid in maintaining a steady rate of flow through the brain. But there is no evidence from experimental work to show that it can cause the arteries to shut down sufficiently to bring about ischemia.

Local increase of blood flow with increase of nervous function. It is a general rule that the organs of the body, when in active function, have more blood flowing through them than when at rest. In order to find out whether this was true also in the brain, Cobb and Talbott (10) in 1927 made experiments on cats which were intravitally injected with Berlin blue, while inhaling a strong-smelling gas and secondly while inhaling air as a control. In the cats in which the olfactory nerves were stimulated, the olfactory bulbs showed 55 per cent more injected capillaries than in the controls. In other words, the evidence indicated that there was more blood flow to an area in the brain where stimulation was causing increased neuronal activity. In 1937 Gerard (11) found local temperature changes indicated increased blood flow in the visual areas of the brain after stimulating the eye with light. He also found an increased blood flow in the olfactory area after inhalation of ammonia and in the sensory area after massaging the paw of a cat. Using a similar method, Schmidt in 1936 (12) found areas on the mesial aspects of the occipital lobe where increased blood flow followed stimulation of the retina. He believes that this change is due to the activity of the nerve cells and that the mechanism causing the vasodilatation is not neural but chemical. The most probable explanation is that the active nerve cells produce locally increased concentrations of carbon dioxide which acts as a vasodilator.

Cerebral circulation and the electroencephalograph. The electrical activity of the brain which can be recorded by means of the electroencephalograph arises from discharging cortical neurons. Apparently contraction or expansion of the musculature of the cerebral arterioles plays no part in this cortical activity; for instance overventilation, which causes constriction of these arteries, does not produce the very fast waves which accompany muscular contractions.

The brain waves are radically altered by changes in the chemical composition of the blood which traverses the brain. Circulatory changes are usually of secondary rather than of primary importance. Thus, changes in circulation due to extrinsic causes which are not extensive enough to threaten consciousness have relatively little influence on brain waves. Increase or decrease of systemic blood pressure, or alteration of heart rate with consequent alteration of the cerebral blood flow, have not been shown to influence brain waves. The cerebral circulatory changes may reflect an effort to protect the brain against too great alteration of blood flowing through it.

An example of this is the pronounced slowing of brain waves which occurs with overventilation of the lungs. Such overventilation causes constriction of cerebral arterioles and pronounced slowing of blood flow. Davis (13) has blamed the resulting cerebral anoxia for the cortical bradyrhythmia. Gibbs and associates (14) on the other hand, correlate the slowing with the reduced carbon dioxide tension of the brain. Their observations, backed by measurement of the cerebral A-V oxygen and carbon dioxide differences on unanesthetized human subjects, indicate that the high voltage slow waves of the E.E.G. occur in persons whose cerebral arterioles fail to constrict with overventilation. Constriction prevents the CO_2 from falling as much in the vein as it does in the artery and hence maintains a relatively steady level of CO_2 in the capillaries and in the brain cells. A steady level of CO_2 appears to be of more importance than a steady level of oxygen or of sugar in the maintenance of normal brain waves. This conclusion is further strengthened by the fact that if subjects breathe air containing only four per cent of oxygen brain waves are slowed. But if carbon dioxide is added to the mixture, the frequency of the brain waves becomes normal in spite of the profound anoxemia (14).

The question of clinical arteriospasm in the brain. Spasm of the cerebral arteries or arterioles has been rarely observed in laboratory animals and man. In 1859 Kussmaul and Tenner reported that convulsions could be produced in rabbits by electric stimulation of the cervical sympathetic nerve. This experiment has been repeated innumerable times since then but only occasionally have the rabbits showed a convulsive reaction. Schmidt (15) has shown that stimulation of the cervical sympathetic nerve in the rabbit may cause dyspnoea and extensor muscular spasm but he emphasizes that this excessive activity only occurs under abnormal conditions and points out that it may depend on contraction of the internal carotid outside the skull. The observation, however, started much speculation as to the rôle of the cerebral artery spasm in the production of brief neurological symptoms. A few observers have seen obliterating vasoconstriction in laboratory animals but these were under distinctly pathological conditions. Under any experimental conditions that approached normal the cerebral vessels have shown only slight contraction when the vessels of the skin of the ear, for example, would show marked constriction. Nevertheless it has been established that there is a vasoconstrictor innervation of the cerebral vessels, and this leaves the possibility that under abnormal conditions there may be cerebral vascular spasm sufficient to cause symptoms. A few cases of epilepsy that showed marked vasomotor symptoms have been relieved by sympathetic denervation of the cerebral arteries, but there have been many more negative results from these operations than positive. There are some well documented cases where patients with Raynaud's disease of the extremities have shown convulsions during attacks of vascular spasm which were visible in the hands or feet. The supposition is that there is also vascular spasm of the brain.

Although proof is lacking there is enough clinical evidence to justify the suspicion that cerebral vascular spasm occasionally occurs in man, causing short periods of convulsions, hemianopsia, aphasia, paralysis, confusion, and the like.

Syncope. Syncope from cerebral anemia is directly due to extracerebral causes, a primary dilatation of peripheral capillaries or veins, with pooling of blood in them and consequent cerebral anemia. However, as in many other extrinsic situations, the primary dysfunction of the autonomic nervous system has its representation within the brain. The loss of consciousness is accompanied by an abrupt fall of cerebral blood flow and the O_2 saturation of blood leaving the brain becomes less than 30 per cent (Lennox and Gibbs 16).

An additional mechanism is present in patients with an irritable carotid sinus. The paper by Ferris, Capps and Weiss (17) in 1935 divides the reaction to pressure on the sinus into three types according to the physiological mechanism: the vagal type caused by standstill of the heart, the depressor type caused by general vasodilatation, and the cerebral type probably due to "cerebral vasomotor changes or reflex influences on certain brain centers." Weiss apparently believed that "localized areas exist in the brain for the regulation of the conscious state" that may be likened to the "respiratory center." With this we do not agree, believing that consciousness is represented at several levels of the central nervous system, and that it is not a matter of one's being "conscious" or "unconscious," but of being either more or less aware of the environment. Attacks of the cerebral type oftentimes suggest hysteria. This group of cases in whom no failure of circula-

tion is observable might be explained by vasoconstriction in the brain, but the evidence is against this. In the first place the loss of consciousness comes on too suddenly to be readily explained by such a mechanism, and secondly, there is no change in total cerebral blood flow as judged by cerebral arteriovenous oxygen differences. Since we do not believe that consciousness is controlled by centers which can be switched on and off by reflexes, the remaining possibility seems to be that stimuli from local areas of ischemia, or from stimulation of end organs in the carotid sinus, heart and great vessels, may induce discharges of neurons in the cerebral cortex which spread like the epileptic discharge and blot out consciousness in a few seconds. The similarity of the carotid sinus syndrome described by Weiss to a mild epileptic fit may be striking.

Cerebral circulation and epilepsy. Spontaneous epileptic seizures in man are not preceded by slowing of the total circulation of the brain as indicated by a flow recorder placed in an internal jugular vein (18). A greatly increased flow accompanies the convulsion as a result of the increased blood pressure, but there is no change in flow during petit mal. The possibility of spasm of a single or of a few arterioles in certain special cases has not been excluded, though demonstration in epilepsy of intermittent or, in some cases, continuous and generalized cortical dysrhythmia argues against an occasional localized arterial spasm.

In direct observations of the human cortex, Penfield (19) observed the phenomenon of arterial-looking blood leaving the site of the brain involved in a focal discharge. This might be explained most readily by assuming that the excess activity of cortical cells caused an increased local supply of CO_2 which caused dilatation of cerebral arterioles in that area; such effect would be a result rather than a cause of the seizures. Penfield's histological studies of traumatic epilepsy convince him that thrombosis of small vessels at the periphery of a cerebral lesion may cause progressive extension of the lesion and result in abnormally functioning neurons and seizure discharges. Studies by Nims and associates (20) of arterial and internal jugular blood suggest that patients subject to petit mal do not have normal chemical control of cerebral arterioles. Overventilation in such patients is not accompanied by prompt constriction.

Cerebral circulation and migraine. Unlike epilepsy, attacks of migraine are accompanied by symptoms which strongly suggest involvement of cerebral vessels—pallor or flushing of the face, pain which may throb synchronously with the heart beat, transient scotoma, hemianopsia, hemiparesis and parasthesia. Most clinicians have assumed that the pain was due to constriction of arteries of the head. Lennox and his associates in analyzing the relief of pain from use of ergotamine tartrate, which causes constriction of cranial vessels, suggested that pain was associated with undue relaxation of arteries. This explanation has had experimental proof at the hands of Wolff (21) and his associates. They attribute cranial pain to a dilatation of branches of the external carotid and cerebral symptoms such as hemianopsia and hemiparesis to constriction of arteries in the brain. This last explanation rests on the observation of relief of visual disturbance by inhalation of the dilator drug, amyl nitrite. Milder vaso-constrictor effects are secured also by ingestion of caffeine and inhalation of oxygen. Because ergotamine tartrate stops the symptoms attributed by Wolff to constriction, this drug must have a differential effect on branches of the external and the internal carotid arteries. In rare instances, persons subject to prolonged migraine have suffered neurological damage as a result of thrombosis of cerebral or retinal vessels, apparently the sequelae of a spasm of these vessels. The whole phenomenon of migraine is closely related to the sympathetic nervous system but interruption of nerve supply to cranial vessels is only occasionally beneficial.

Hypertension. Many authors have pointed out that emotional stress may cause hypertension. This is obvious in the case of the transient elevations of blood-pressure observed in persons who are scared or angry. The mechanism is probably that described by Cannon as a sympathetic discharge preparing the organism for flight or fight. It is not known, however, that this sort of reaction has anything to do with the disease known as "essential hypertension;" this is an easy assumption, but it entirely lacks proof. In fact one could argue that the persons with labile blood-pressure are just the ones who do not develop the permanent and incapacitating "essential" hypertensions. The cerebral circulation probably plays no rôle in either of these conditions; in the "essential" cases the circulation of the kidneys is impaired. Patients with hypertension examined by Williams and Lennox (22) had a slightly increased cerebral A-V oxygen difference, indicating that cerebral vessels participated in the vasoconstriction.

Cerebral hemorrhage. Frank bleeding into the brain from an artery or vein is related largely to lesions of the vessel walls from sclerosis, infection or trauma. The dynamics of the cerebral circulation must play a rôle, especially in locating the lesion, because pressure is higher, for example, in small arteries that arise from large trunks, and at the points of branching, than in equally small arteries farther out on the tree. There is also the factor of how well the arterial wall is supported by surrounding tissue, and at what pressure. The

theory that gross cerebral hemorrhage takes place only from vessels that lie in softened brain substances is not only unproven but unreasonable. If partial softening of brain substance did take place about arteries, the fluid and soft brain would surround the vessel at a pressure practically as great as that of the normal brain, i.e., 150 mm. of water, whereas the pressure within the artery would be about 1500 mm. of water. It is apparent that what keeps the blood from bursting out is not the support of the surrounding brain or fluid, but the elastic and muscular coats of the artery wall. Hemorrhage from veins is a different story. The blood within them is at a low pressure, only slightly above cerebrospinal fluid pressure, so changes in the latter, from whatever cause, may increase or decrease the likelihood of continued venous hemorrhage. The formation of subdural clots which slowly increase in size is a case in point. There is the general rise in intracranial and venous pressure along with the local changes in osmotic relations at the site of the clot.

Encephalomalacia. "Cerebral softening" and "cerebral hemorrhage" are not such distinct entities as one usually supposes. Probably all infarcts of the brain, severe enough to cause softening, are accompanied by some extravasation of red blood cells. Just when this capillary extravasation becomes worthy of the name hemorrhage is an unsettled question, but most of the perivascular "ring-hemorrhages" of the brain are of this type. Infarcts in other organs begin by being red or hemorrhagic, later they become white or anemic. Chase in his experiments with mesenteric emboli shows that red areas develop by diapedesis of erythrocytes from dilated capillaries and venules beyond arteriolar constrictions. Greenfield believes that cortical infarcts are originally always red and infarcts of white matter are white, both in the cerebrum and cerebellum. He has demonstrated that 24 hours after ligation of a cerebral artery there was red infarction of the cortex with neighboring white infarction of the white matter. This means that there is little anastomosis in the white matter, but enough in the gray to make blood flow from normal areas into the anoxic and dilated capillaries of the infarcted area. It is probable that at least one-twentieth of the normal blood supply of an area must reach it after infarction to cause diapedesis and "red infarction." Evans thinks the varying degree and the varying suddenness of oxygen deprivation is more important: red infarction takes place when circulation is merely slowed; complete sudden occlusion leads to white necrosis and cyst formation. Tureen's experiments on the spinal cord demonstrate that fifteen minutes of occlusion of the aorta will cause lesions of spinal nerve cells. In the brain 3 minutes and 25 seconds of anemia will cause necrosis of cortical cells (4).

Ricker (23) believed that the nervous control of the vessels played an important part in causing cerebral lesions, such as small focal softenings, but Forbes' demonstration that in normal brains the control is but slight as compared to other organs makes this unlikely. It is probable, however, that in scars and sclerotic or otherwise diseased areas, stimulation by vasomotor nerves may be abnormal and might cause occluding spasms of the vessels and foci of necrosis.

Trauma. There are some strong proponents of the theory that vasoparalysis quickly follows a blow to the head and causes many of the phenomena that result therefrom (24). This certainly cannot account for the loss of consciousness, which takes place instantly, since unconsciousness from stopping the cerebral blood flow takes from 5 to 7 seconds. A blow, however, might cause vascular paralysis with dilatation of the small vessels, stasis, relative anoxia and extravasation of fluid and erythrocytes. Such a series of events could well explain the perivascular hemorrhages and edema seen in microscopical sections from brains which had suffered a contusion. More severe injury might add laceration to this picture, with ruptured vessels and obvious hemorrhage. The small arteries might stop bleeding because of the local spasm following direct trauma seen by many investigators; the veins would probably clot during the stasis caused by rising intracranial pressure.

The main question is, however, does a blow to the skull cause vasoparalysis, and, if so, how? Knocking out the rather weak vasomotor innervation would not seem likely to cause significant dilatation. It seems more probable that stasis from other causes sets up the chemical asphyxial reactions that make the vessels dilate and exude plasma and cells.

Aside from the hemorrhages and edema seen at autopsy, no circulatory phenomena are known to be especially related to cerebral injury except the increase in venous outflow noted by Denny-Brown (25). This is probably the result of vasodilatation, but what causes the dilatation is not known, although it might come partly from vagal stimulation (7). Of course when there is enough local injury by contusion to cause swelling, the intracranial pressure rises and the venous pressure must rise to a slightly higher level in order to keep blood flowing out of the cranial cavity. This accommodation is easily made until the cerebrospinal fluid pressure reaches a level approximating arterial pressure. Then a re-adjustment upwards is made and the Cushing phenomenon (26) appears. In clinical practice, however, this is rarely seen except where rapidly expanding le-

sions raise the pressure 800 or 900 mm. of water in a few hours.

Vasconstrictor and vasodilator drugs. Except for the work with epinephrine the action of drugs on the vessels of the brain has been little studied by reliable and well controlled methods. Schmidt (15) reports observations both by the thermocouple-blood-flow technique for recording local changes of flow in brain tissue, and by the "thermostromuhr" on the carotid artery for estimating total blood flow through the brain. Nitroglycerine is an effective local and general dilator, histamine is irregular in its effect, but usually dilates, ergotamine is the only local constrictor. It acts slowly and only in large doses, but causes no decrease in total blood flow. Pool, Nason and Forbes, observing living vessels under the microscope, saw the vessels of the dura contract regularly 20 to 35 per cent of their diameter after intravenous injection of epinephrine, pitressin and ergotamine. In the arteries of the pia the effect was usually a slight dilatation. Thomas has shown that alcohol dilates cerebral vessels conspicuously. In some of the experiments the sudden and marked fall in blood pressure may have caused the vasodilatation, subsequent work of Forbes having shown that a drop in blood pressure to a critical level causes dilatation of vessels, no matter what the cause of the fall.

Other experiments have shown that narcotic drugs usually cause vasodilation of cerebral arteries (ether, chloroform, amytal, phenobarbital). Morphine had little or no effect upon the vessels unless the blood pressure fell sharply and then there was slight dilatation. Avertin, however, regularly caused a distinct vasoconstriction in spite of the fall in blood pressure. The convulsant drugs had varied effects upon the vessels. Caffeine in large doses caused convulsions with vasoconstriction; absinth in small doses caused constriction of the pial arteries, in larger doses, dilatation; homocamfin and picrotoxin usually made the artery constrict slightly, while camphor monobromate caused dilatation before the convulsion.

The foregoing observations were made in animals. In man, Gibbs, Gibbs and Lennox (27) using a thermo-electric flow recorder in an internal jugular vein and measuring cerebral A-V oxygen differences, found amyl nitrite, histamine, ether, adrenaline and ergotamine caused an increased flow, only the last two due to increased blood pressure; the decreased flow with caffeine was perhaps due to stimulation of respiration. Sedative drugs producing sleep, as well as normal and narcoleptic sleep, caused no noticeable change of blood flow if the blood pressure remained steady. The ideal drug to counteract cerebral ischaemia would be one which dilates cerebral vessels and raises blood pressure. Carbon dioxide most nearly comes up to these specifications and should be tried clinically. Among vasodilator drugs the xanthines (especially theophylline) seem most suitable. Schmidt has used nitroglycerine and acetyl-B-methylcholin with beneficial effects for the Cheyne Stokes respiration of uremia, and for the apnea and periodic respiration following hyperpnea. We have given large doses of alcohol by mouth in cases that showed the earliest symptoms of aphasia and hemiplegia and believe that we have thus aborted some such attacks, but proof is impossible (28). It would seem worth while for physicians to watch for early cases of cerebral ischaemia, including thrombosis and embolism, and be more willing to try vasodilator therapy. The important point is to increase blood flow in the brain so absolute rest is not desirable and morphine is strongly contra-indicated.

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The American Institute of Nutrition

George R. Cowgill, Chairman

SYMPOSIUM ON HUMAN VITAMIN REQUIREMENTS

INTRODUCTION

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It is now three years since the National Nutrition Conference accepted a table of recommended allowances for most of the better known dietary essentials. All published evidence on the requirements for the different factors was critically examined and appraised and many nutritional authorities were consulted before the final table was compiled. Dr. Lydia J. Roberts presented much of this evidence before the 1941 Chicago meeting of the Institute of Nutrition and obtained additional suggestions at that time.

During the past three years the recommended dietary allowances have been widely used and accepted. There has been much discussion and some criticism of the accuracy of the individual values which is fortunate because it is only by this means that further improvements can be made. This discussion and the realization that much more information is needed have stimulated extensive experimental work especially on the vitamin requirements of human subjects. Since many of these results would have been presented at the annual meetings of the American Institute of Nutrition if it had been possible to hold such meetings, it is logical that this published symposium on "Further Studies on Human Vitamin Requirements" be sponsored by the Institute.

Each of the following reviews has been prepared by an authority actively engaged in research dealing with the specific vitamin in question. The information summarized in these papers will not only be helpful to the Food and Nutrition Board in future deliberations on possible modifications of the dietary allowances but will indicate more clearly where additional work is especially needed.

It is doubtful that we will ever have unanimous agreement on exact quantitative values for the requirement of all our dietary essentials, but greater progress will be made if the type of requirement is clearly understood by everyone concerned. Many have considered the established dietary allowances to be minimum values while others have interpreted them correctly as optimum values which should be met if possible. Thus minimum figures obtained by accurate scientific measurements under specific conditions may be quite different from dietary allowances. In the latter case numerous variables must be taken into account which are automatically eliminated in the more accurately controlled experiments. In order to compensate for these variables some degree of safety must be incorporated into the values suggested for practical purposes. Some degree of safety is always recognized in experimental work. Several years ago work in our laboratory convinced us that the minimum thiamine requirement of the rat was about 100γ per 100 grams of ration (incidentally this level is equal to 0.2 to 0.25 mgm. per 1000 Cal. which is near the value considered to be the minimum for humans) however we have never used this low level in diets of rats maintained for other studies. We have always used 200 to 300γ and some laboratories have used 500γ or more per 100 grams of ration. If we are this generous with rats we should not object to a somewhat similar ratio in practical human nutrition. How-

ever, the mere multiplication of the minimum value by a generous factor does not necessarily insure safety.

Many factors are operative under practical conditions and some of these variables become evident in the work reviewed in the following papers. To date only a relatively small segment of our whole population has been studied but even so age, sex, environmental conditions and type of diet show their effect. In experimental studies both with animals and humans rather standard diets have been used. If there is only one characteristic about our present day diet it is the diversity of food consumed from day to day. This continual change in ingested material undoubtedly affects the intestinal flora and therefore the production and destruction of some of the vitamins.

Most nutritional experiments have been of short duration. Even animal experiments have suffered in this respect. However, it is gratifying that some of the most recent human experiments are being extended over many months. The question has been asked, how long must a human experiment be continued in order to be valid. That remains to be answered but I might add our recent experience with one of our monkeys. He was placed on a purified but apparently adequate diet 3½ years ago. After one year he had made a perfect record and we thought this period should be sufficient to prove the adequacy of the diet. However, he was continued or another year and then for still another year. At the end of the three years we decided there could be no question about the results. Leaving the diet constant the environmental conditions were changed and within a relatively short time the animal showed deterioration. With some difficulty the animal was brought back to normal and we are now quite willing to leave him for still another year.

I am sure that the following reviews will not only give us additional scientific facts but will emphasize the complexity of the problem. We must critically appraise all the scientific evidence but we must also be willing to accept reasonable working values until more facts are available.

THE HUMAN REQUIREMENT FOR NICOTINIC ACID

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Our knowledge of the human requirement for nicotinic acid is extremely scanty. The National Research Council in compiling its Table of Recommended Dietary Allowances of the nutrients was faced with the need to suggest a level of intake for nicotinic acid before any direct evidence about minimum requirement was available. The figure agreed on was 18 mgm. daily for a moderately active man of 70 kgm., and there is at present no reason to suggest any other figure until much more evidence is available. The plausible assumption was made, again in the absence of direct evidence, that the requirement varies with energy expenditure.

Until it is possible to observe the development and cure of nicotinic acid deficiency conditions in human beings on rigidly controlled diets (as has been reported for corresponding experiments on thiamin (1)) it will be impossible to determine precisely the minimal requirement of any individual, or the effect of interaction of other vitamin deficiencies, dietary factors and environmental conditions. Because deficiencies of other B vitamins are likely to accompany nicotinic acid deficiency, their effect on nicotinic acid requirement is an important practical problem. Another point to be settled before satisfactory determination of requirement can be made concerns the means of recognizing nicotinic acid deficiency. It is relatively easy to detect such deficiency when it has resulted in classical pellagra, but it is not certain whether pellagra always appears as a result of severe nicotinic acid deficiency, nor is it easy to detect with confidence slighter degrees of deficiency.

There appear to be no published reports of experimental work designed to determine the human requirements of nicotinic acid. Schaefer, McKibbin and Elvehjem (2) have found the nicotinic acid requirements of 4 dogs to lie within the limits 200–225 micrograms per kgm. body weight. From this they calculated the minimum requirement of a 70 kgm. man as 10 mgm. daily, on the assumption that the requirement is parallel to output of energy by the organism. Since it has been shown by Sarett, Huff and Perlzweig (3) that there are differences in the ways in which man and the dog metabolize nicotinic acid, this calculation may possibly not be valid.

Determination of customary intakes of nicotinic acid. The remaining quantitative information bearing on human nicotinic acid requirement comes from dietary surveys in which customary intakes are estimated or actually measured. Most

frequently individual or average diets are either estimated or weighed and the nicotinic acid content of these diets calculated with the aid of a table of the nicotinic acid content of foodstuffs. Such calculations, like the food tables themselves, are apt to provoke one of two reactions. As Widdowson and McCance have remarked, there are two schools of thought—"one tends to regard the figures in them as having the accuracy of atomic weight determinations; the other dismisses them as valueless. . . The truth of course lies somewhere between these points of view." (4)

Results from dietary calculations. Aykroyd and Swaminathan (5) by such methods found that in India a typical poor rice-eater's diet provided 5 mgm. nicotinic acid daily if the rice were raw-milled or 11 mgm. if it were parboiled. Yet pellagra is rare among that impoverished rice-eating population.

Kodicek (6) calculated in this way that the wartime diet in Great Britain provided on the average 12.2 mgm. nicotinic acid daily for whole-meal bread consumers and 9.0 mgm. daily for white bread consumers (the majority of the people) before the National Wheatmeal Bread replaced all other types in 1942. Pellagra is almost unknown in Great Britain.

In this country, Cheldelin and Williams (7) reported that in an average 2500 calorie American diet "such as was consumed by the middle two-thirds or three-fourths of the population prior to the use of enriched bread and flour," the amount of nicotinic acid was 11 mgm. Youmans and coworkers (8) in a dietary survey made in Tennessee calculated that over half of the white and three-fourths of the colored population consumed less than 10 mgm. daily; and one-fourth and two-fifths respectively consumed less than 6 mgm. A dietary survey in Wayne County, N. Carolina (9) made in 1942 before the use of enriched flour and bread in this section, revealed an average daily intake of food which I have calculated to contain 7.2 mgm. of nicotinic acid. One-sixth of all subjects over 15 years old consumed less than 5 mgm. daily; for males and females of this age group, the mean daily intakes were 8.1 mgm. and 7.9 mgm. respectively. No pellagra was observed in the clinical examination of 840 subjects whose diets were recorded[1], nor were any other gross signs of milder nicotinic acid deficiency observed. There is no reason to believe that the diets have recently changed for the worse and that more pellagra is soon to be expected in this region; on the contrary the vital statistics show that pellagra has decreased steadily in this county from 250 cases and 88 deaths in 1930, almost to a vanishing point in 1942 (10).

It is of interest to consider the nicotinic acid intake of the male subjects in whom Goldberger and Wheeler (11) produced pellagra experimentally. Tables 9–16 of their paper give for 8 of the 28 weeks of the experiment the quantities of all foods consumed by the experimental subjects. From these tables one can calculate that the average nicotinic acid intake per man per day, assuming no loss in cooking, was 7.2 mgm. The food consumption of the control subjects is not presented in the same detail, but from tables 4-7 one can obtain an estimate of 11.9 mgm. nicotinic acid per man per day ingested during four weeks. It is implicit in the data that this is an overestimate, compared with a true estimate for the experimental subjects. Goldberger's pellagrins thus had the same mean nicotinic acid intake as the Wayne County subjects reported above, but the following points of contrast should be noted. These pellagrins ing[illegible] for [illegible]ith a mean calorie value 50 per cent greater [illegible]n the Wayne County subjects yet lost weight at an average rate of 0.75 lb. weekly; they had much more corn in their diet (28 per cent of their calories came from cornmeal and grits) and protein provided only 6 per cent of their calories compared with 12.5 per cent.

Results from analysis of duplicate diets. The results recorded above were all obtained by calculation from estimated or weighed diets. Winters and Leslie (12) have obtained more reliable figures for nicotinic acid intake by direct measurement. They collected duplicates of all the meals, drinks and snacks taken by their subjects (two groups of women) on their self-chosen regular diets, for periods of 7 to 21 days. Each day's sample was homogenized in water and an aliquot taken for estimation of the nicotinic acid by the microbiological assay of Snell and Wright (13). Among 24 women from low-income groups in Austin, Texas, the daily intake of nicotinic acid ranged from 2.7 to 9.8 mgm. with a mean of 4.2 mgm. For 11 Anglo-Americans, 7 Latin-Americans and 6 Negroes the means were 6.4, 3.1 and 4.1 mgm. respectively. Fifteen of the subjects were examined clinically; no pellagra was observed but nine were stated to show milder signs of nicotinic acid deficiency, by criteria about which there is no general agreement (see below). These signs were not seen in any subject whose intake was greater than 5.9 mgm. per day. Among 20 women of a moderate-income group the intake ranged from 5.5 to 11.4 mgm. daily with a mean of 9.1 mgm.; no clinical examination was made of these subjects.

Winters and Leslie suggest the possibility that the recommended allowances have been placed too high. This possibility is also supported by the

[1] The calculation of the average intake was made from a statistically suitably weighted sample containing 10% of all the diet records.

less rigorous results of the workers who have not actually analyzed the meals of their subjects. It appears probable that when the time comes to revise the recommended allowance of nicotinic acid, it will be somewhat decreased.

Factors affecting nicotinic acid requirement. As mentioned above, it seems likely that the requirement will vary with the energy expenditure of the subject. It may also be modified by other factors, particularly by the major cereal of the diet. Aykroyd (14) pointed out in 1930 that although pellagra is "almost invariably associated with the consumption of maize", neither rice nor millet shows any superiority over maize (corn) as a source of vitamin B_2. More recently Aykroyd and Swaminathan (5) have calculated that a typical maize diet consumed in a pellagrous district in Moldavia gave a nicotinic acid intake of 15 mgm. daily. This is higher than the 5 mgm. level which they calculated for rice eaters in India (where pellagra was rare), and suggests that on a maize diet more nicotinic acid is required to prevent pellagra.

This finding directs attention again to the historical connection between maize-eating and pellagra: a connection which led Chick (15) to combine several apparently mutually exclusive theories into the hypothesis that "Pellagra is caused by a toxic substance derived from the maize diet, which can be corrected by sufficient 'good' protein, or perhaps by sufficient vitamin B_1 (which is found to accompany the 'good' protein)." This hypothesis is attractive today if we substitute nicotinic acid for the vitamin B_2 of Chick. It is supported by recent work from this laboratory on the analogous canine disease blacktongue (16, 17); but of course it remains no more than a working hypothesis.

If it should be established as correct, it will mean that on some diets nicotinic acid deficiency, however severe, will not regularly produce the classical syndrome of pellagra. For this reason, and also to diagnose lesser degrees of nicotinic acid deficiency on diets which ultimately would lead to pellagra, there is an acute need for recognition of nicotinic acid deficiency which has not produced pellagra. Clinical criteria have been proposed by Kruse (18) and by Jolliffe and Stern (19) but these have been rejected by Ruffin (20). In any case there is no general agreement upon such criteria, and studies of the requirement cannot be interpreted without them. Excretion studies will not solve the problem until they in turn can be evaluated in terms of clinical criteria.

Summary. There is insufficient evidence to justify alteration of the National Research Council's Recommended Dietary Allowance of nicotinic acid, but sufficient to suggest that the figure is somewhat too high. Evidence from dietary surveys suggests that the minimum requirement of a 70 kgm. man is probably less than 10 mgm. When the chief cereal of the diet is corn (maize) the requirement for nicotinic acid is probably increased. We must await the discovery of valid methods of diagnosing human nicotinic acid deficiency which does not take the form of pellagra, before progress can be made toward determining the requirement more accurately, or determining what factors affect it.

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FURTHER STUDIES ON HUMAN REQUIREMENTS FOR RIBOFLAVIN

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Within the past year, two outstanding metabolic studies on the human requirements for riboflavin have been reported. The first, from the Mayo Clinic, (1) records data on four groups of institutionalized subjects on quantitative diets for periods of from 246 to 288 days, with a preliminary period of high riboflavin intake. One group of four subjects was maintained for 288 days on a diet presumably adequate in all factors except for riboflavin, which was supplied by the diet as 0.35 mgm. per 1000 Calories or a total of 0.7 mgm. per person per day. This level is probably representative of the diet of certain population groups in this country.

None of the ocular, cutaneous, oral, or lingual manifestations which have been widely accepted as evidence of certain degrees of ariboflavinosis occurred; physical and neurological examinations were negative. For the period of restricted intake, as a whole, an average of 14 per cent of the dietary riboflavin appeared in the urine of the four subjects. Averages of the excretions for the three subjects who were tested at like intervals are plotted against time for a period comparable in length to that used in the next study to be reported (fig. 1). The trend gives strong evidence of a continued depletion of tissue stores of riboflavin at this level of intake over such a period.

Most, if not all, of the cases of spontaneous human deficiency diseases involve the lack of more than one vitamin. That this might influence specific avitaminoses was suggested by the work of Sure and Ford (2) who restricted thiamine in the diets of rats and noted that the total urinary and fecal elimination of riboflavin increased two to seven fold over that of the control animals, mainly because of poor absorption and an excretion of some of the stored riboflavin. Sure conjectures that the prevalence of thiamine deficiency in this country might be found to be significant in precipitating manifestations of riboflavin deficiency in borderline human cases.

In the metabolic study of the Mayo Clinic, one group of subjects was given the basal diet without the B complex supplement which had been given to Group I. Symptoms and metabolic defects typical of thiamine deficiency appeared in this group and were readily relieved with adequate thiamine administration. However, no influence was apparently exerted on the rate of depletion of tissue stores of riboflavin by this simultaneous restriction of thiamine and possibly other members of the vitamin B complex (fig. 1). This is in agreement with the observations of Ferrebee and Weissman (3) who attributed no clinical significance to thiamine lack in the production of riboflavin deficiency, inasmuch as such influences on riboflavin balances as were demonstrated by Sure (2) are believed by them to be true only in terminal stages and are of no great importance.

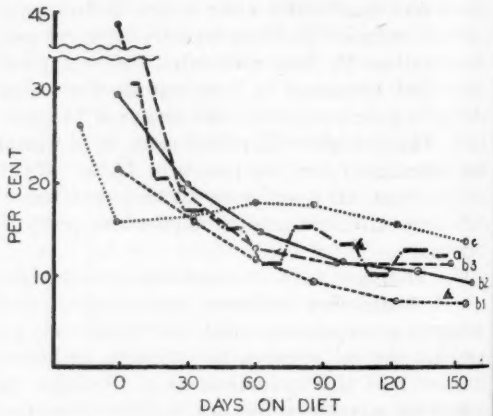

Fig. 1. Per cent of riboflavin intake excreted in the urine.

(a) Keys' 3 subjects, 152 days on 0.99 mgm. total riboflavin, 0.31 mgm. per 1000 Cal.

—— -·- regular 24 hr. collections.

△ "saturation test" with 1 mgm. added, 24 hr. collection.

(b-1 to -3) Mayo Clinic "saturation test" 4 hr. collection after 2 mg. intraperitoneally.

--------- (b-1) Group I, 3 subjects 0.7 mg. total flavin, 0.35 mgm. per 1000 Calories.

— — — (b-3) Group II, 2 subjects, same dose flavin, no other B-complex supplement.

——— (b-2) Group IV, 5 subjects, 1.0 mgm. total flavin, 0.5 mgm. per 1000 Calories.

..... (c) Mayo Clinic Group I, assays on 24 hr. collection.

The effect on riboflavin balance of high levels of thiamine intake, on the other hand, were also investigated by Klopp, Abel and Rhoads (4). A direct relationship existed between the thiamine administered and the proportion of riboflavin excreted by certain of their human subjects, possibly related to the phenomenon reported by Supplee and his associates (5) of a mobilization of riboflavin from the tissues into the liver influenced by thiamine; nevertheless, the influence was transient and no indication was detected of any deficiency of riboflavin in body stores through

the daily administration of large amounts of thiamine for as long as 73 days.

For two other groups of the Mayo Clinic subjects, the intake of riboflavin was increased over that in groups 1 and 2; in one group, (which had been planned as a part of a different study) the level was raised to 0.5 mgm. per 1000 Calories chiefly by a change in the type of bread from that used for groups 1 and 2. No clear-cut symptoms of deficiency were observed. The riboflavin stores at the end of the study were thought to be better than for groups 1 and 2, although there was evidence here also of progressively lessened output (fig. 1). In the fourth group, supplements of 1, 2 and 3 mgm. of riboflavin were given. When the total intake was held at 1.6 mgm. per day, or 0.8 mgm. per 1000 Calories, for a period of 45 days, the excretion of "saturation" test doses seemed to indicate that this level was not associated with depletion of tissue stores. It was, therefore, concluded that the minimal requirements of these subjects for riboflavin did not exceed 0.8 mgm. per 1000 Calories and probably was nearer 0.5 than 0.8 mgm.

In contrast to the use of very sedentary subjects in the first study, the second study was carried out on very active young men by Keys and his associates (6) to test whether any abnormality of work performance would be occasioned by a restriction of the dietary riboflavin to an intake as low as one-third of the National Research Council's recommended allowance. The six subjects were cooperative graduate students in a good state of physical training; these were transferred directly from their accustomed boarding house fare to the restricted weighed diet containing 0.31 mgm. of riboflavin per 1000 Calories or 0.99 mgm. per person per day, a total amount about 50 per cent above that in the Mayo Clinic study, although 12 per cent less in relation to Calories. Three subjects continued the diet for 84 days and three for 152 days. For the latter subjects, this depletion was followed by a period of 26 days of supercharging with 11.2 mgm. of riboflavin and then a return to the low level for further tests. At intervals during 5 succeeding weeks on the boarding house fare, the urinary excretion was determined.

The average proportion of the dietary riboflavin which appeared in the urine during the depletion period as a whole (12 per cent) was of the same order of magnitude as in the previous study. The percentage output declined from a level of 23 in the first few days of the depletion to the general level of 10–14 per cent within about a month and a half. The results were considered to indicate a lower apparent saturation than that of the Mayo subjects. However, the importance of such a depletion of tissue stores was emphatically discounted by the authors, inasmuch as the output seemed to be so readily stabilized at the lower level for at least half of the depletion period of five months, and as the urinary excretion rose so abruptly when the intake of riboflavin was increased, i.e., to 54 per cent of the intake of 11.2 mgm., within one week. It must be admitted that the significance of this test of recharging body stores was largely obscured by the excessive dosage of riboflavin employed.

Although the body was thus shown to be capable of accumulating reserves of riboflavin, the very swiftness of its loss indicated to the authors that the reserve was not great. Furthermore, there were no detectable penalties for this loss of reserve riboflavin, within the duration of the experiment, except a low excretion rate, inasmuch as in the case of these six subjects "work performance and the bodily responses to work were essentially unaffected by the dietary alterations". This lack of effect on work performance of low flavin was confirmed by a further experiment (7) in which the relative riboflavin intake was dropped to 0.15 mg. per 100 Calories for 14 days on hard work (4800 Cal. daily).

In comparing the results of the two studies in figure 1, one is struck with the similarity of the general trends. Graphically presented, the percentage excretion values give an impression that after the first rapid depletion there may have been a slower loss for the remainder of the five months depicted, perhaps from a different type of tissue stores. To establish that such a trend is without significance would probably require prolonged and thorough experiments and observation. Hence, while the meticulous work of these studies has given ample assurance that over several months' time even very active adults, if not previously depleted, will not show measurable harm from the restriction of the intake of riboflavin to a level far below the recommended allowance, nevertheless, as was pointed out by the authors themselves, the results are not intended to answer the question of possible effects of long continued use of such levels. This implication will be referred to again.

A noteworthy feature of the results was the absence of cheilosis and significant changes in the eyes of the various subjects. The minor degree of opacities and vascularization at the limbus observed in five of Keys' six subjects initially did not progress during the depletion period nor did they disappear during the 12 weeks period of restoration. This is the more notable in that the subjects "crammed" for their comprehensive examinations during a part of the depletion period, thus presumably subjecting their eyes to severe strain. It has been the belief of many workers in this field, although now widely questioned, that an

intensive use of the eyes or exposure to glare may create an increased need for riboflavin locally in ocular tissues. The suggestion of such a relationship, at least, was the basis of two recent studies with large groups of human subjects giving evidence of eye strain.

One study (8) was occasioned by the opportunity afforded Tisdall and his associates of examining the nutritional status of the men in the Royal Canadian Air Force, a personnel subjected to extreme conditions of glare and eye strain and at the same time consuming rations found, by assay during a test period, to average only 1.6 mgm. of riboflavin daily. An ideal degree of objectivity in recording the conditions of the eyes was secured by the perfection of a photographic instrument[1] which employed such intense illumination that microscopic details could be clearly recorded by a flash too short to cause discomfort to even sensitive eyes, i.e., one thirty-thousandth of a second. The survey of 198 men classified only one of these (0.5 per cent) as having normal eyes. Perhaps the criteria of normality were set by these investigators at a more exacting level than that of many other workers. Seventeen of the men (8.6 per cent) showed slight proliferation of the limbic plexus, 87 (43.9 per cent) moderate proliferation, and 93 (46.9 per cent) a severe stage of proliferation in which the cornea was penetrated with capillary twigs, streamers and loops. 67 per cent of this group suffered from two or more symptoms which might be referable to eye strain; these were usually worse after flights in bright weather. Seventy of the 93 men were chosen for testing the effects of riboflavin therapy. About one third of these were given only placebos, thus insuring a control group. The other men received 9.9 mgm. of riboflavin taken in three equal doses during the day; a group of 21 men continued this for one month, 28 men for two months.

In view of the statement frequently made that any ocular manifestations actually due to riboflavin lack will disappear under adequate flavin therapy in a few days, it is interesting that only one subject of those treated showed any such rapid improvement. Even in two weeks few of the subjects would have been judged to be improved. On the other hand, after one month, six of the group of 21 men showed a marked or moderate decrease in the degree of vascularization, 14 a slight decrease or doubtful change, and one man, an increase in vascularity. Increasingly pronounced effects were seen after two months in the group of 28 men kept for that time on the dosage. Twenty men now showed marked to moderate improvement, 8 slight or doubtful improvement, and none had become worse. Accompanying these objective changes was a striking improvement in such general symptoms as tiredness of eyes, aching of eyes, and watering of eyes, a sandy feeling under the lids, dizziness, headaches, reading intolerance and decreased visual acuity. Some of the men themselves were surprised to note the improvement as they had considered their former discomfort was to be expected under the conditions present and in no way abnormal (9). In the group receiving only placebos, the results were quite different. There was only faint improvement in any of the subjects in regard to ocular or general symptoms; six subjects became worse.

Some criticisms and comments have been offered by Pirrie (10) on certain features of this paper: that some of the photographs appear out of focus in the printed reproductions; that the degree of improvement indicated by the authors might be questioned, in certain instances, from the evidence presented; that the subjective symptoms might well be attributable to a variety of origins; that the slowness of the responses to therapy in regard to vascularization is unlike the rapid cures reported for advanced riboflavinosis treated with large doses of riboflavin; that no one has demonstrated a connection between riboflavin and snow blindness, which is one well-recognized effect of glare; that the implied incidence of ariboflavinosis in the Canadian population differs markedly from that found in England; and that the diagnosis of ariboflavinosis requires the support of other signs in addition to vascularization. It is to be expected that many of these points will be elucidated by the publication of further work. Pett (11) mentions a survey which was made among the Indians of Northern Manitoba, the report (12) of which is, as yet, not widely accessible. The survey showed an "astonishing incidence" of what appeared to be deficiencies of riboflavin, thiamine and ascorbic acid. The confirmatory studies which were undertaken have not yet been published.

In Toronto, a nutrition survey (13) was carried out on a group of 232 individuals subjected to eye strain under different conditions from those in the previous study, i.e., close continuous use of the eyes in reading under ordinary uniform conditions of lighting. Many of these subjects complained of a sensation of eye strain. Therapy was aimed at evaluating the comparative efficiency of vitamin A and riboflavin in relieving the manifestations. The daily administration of 3 mgm. of riboflavin for ten weeks resulted in an apparent cure of 57 per cent of the 28 cases of corneal vascularization in the group thus treated. This, in itself, might have been accepted as evidence of a much greater effectiveness of riboflavin than of vitamin A, inasmuch as doses of vitamin A led to the loss of conjunctival

[1] The Canadian Research Council has licensed the manufacture of this camera in the United States.

opacities in only 12 per cent of the 32 persons showing this manifestation at the beginning of the treatment. However, of the 57 subjects who showed corneal vascularization at the first examination but were in groups receiving vitamin A or placebos and, hence, no added riboflavin, 42 per cent showed recovery. After deducting this percentage from the original 57 per cent of cures, the authors could point to only 15 per cent of the cases of vascularization in which cures could in fairness be attributed to the riboflavin treatment. However, in the riboflavin-treated group, more relief was experienced from general symptoms of strain, including red and watery eyes, than in the other groups.

In an extensive nutrition survey of 1200 subjects in Tennessee, Youmans and his associates (14, 15) noted a pronounced regression of corneal vascularization in two thirds of the 15 subjects reexamined in the spring after the initial inspections of their eyes, with a slit lamp, in the fall. A change in the intake of riboflavin could not be held accountable for the improvement, inasmuch as diet records indicated that the intake had, in fact, decreased slightly (from 0.63 mgm. to 0.53 mgm. per 1000 Calories) hence, the improvement was attributed tentatively by Youmans and his associates to the decreased ultra-violet and visible light during the winter months. This explanation correlated very well with the observation that virtually no negroes in the region of the survey had decisive corneal vascularization, a fact which might be due to the difference in pigmentation between the two groups, inasmuch as the riboflavin intake was comparable. It was also in harmony with the absence of frank lesions of ariboflavinosis of the tongue, lips or mouth in the white group showing ocular vascularization and with the fact that the occurrence of vascularization in the group of nearly 500 subjects examined with the slit lamp bore no clear relationship to the dietary intake of riboflavin; for, if the exposure of the eye to light was the determining cause in producing a local deficiency of riboflavin, vascularization might well occur independently of these other factors.

The possibility of the destructive action of light on the riboflavin of the eye had seemed to be given an experimental basis earlier by the results of Johnson and Eckardt (16) who accelerated corneal vascularization in rats on a riboflavin-low diet by exposing the heads and eyes to direct sunlight; this was true of a group of rats in which early vascularization was already present and also of a group which had manifested other signs of riboflavin deficiency but not vascularization. Of great interest, therefore, in this regard, is the extensive study of Philpot and Pirie (17) on the distribution and nature of the riboflavin in ox ocular tissues. The distribution was found to be quite uneven. Only traces of flavin were detected in the vitreous and aqueous humors, the lens and the substantia propria of the cornea. From 2 to 3 mgm. per gram of wet tissue were found in the corneal epithelium, ocular conjunctiva, iris ciliary body and choroid. The two richest types of tissue were the retina with 3–4 μg. and the lachrymal and meibomian glands, including the waxy secretion of the latter, with 4–6 μg. per gram of wet tissue. Inasmuch as the corneal epithelium was found to be richer in riboflavin than the blood, one must conclude that the riboflavin is actively secreted either across a membrane, in accordance with the principles stated by Duke-Elder and Davson (18) and as was postulated for ascorbic acid in the intraocular fluid by Friedenwald, Buschke, and Michel (19), or more indirectly through a gland with an external secretion. Because of the relative richness of the lachrymal and meibomian glands in riboflavin, Philpot and Pirie suggested the possibility that the secretion of these glands by bathing the cornea may be one of the sources of its flavin and that ocular lesions due to riboflavin lack may be essentially in the glands themselves, reflected in their secretions. However, such a theory does not seem to be in harmony either with the lack of effect of removing the lachrymal and meibomian glands (17) or with the results of experiments performed by Johnson and Eckardt (16) in which they covered the corneas of riboflavin-deficient rats with ointment or liquid petrolatum and noted that this method of excluding oxygen from the corneal epithelium did not hasten vascularization. Inasmuch as lachrymal secretion was also presumably excluded from the cornea by this procedure, the efficacy not only of atmospheric oxygen but of tears as well, would apparently be called into question.

A direct test was made by Philpot and Pirie (17) of the light-lability of the flavin of ox eyes by exposing them, cooled in ice and bathed in cold saline, to either 1 hour of bright sunlight or to an ultraviolet lamp at a distance of 8 inches. There was no diminution in the riboflavin content of the eyes in either case. This result was not unexpected by the authors because of the fact that in no tissue of the eye assayed by them was the riboflavin in the free form, with the possible exception that a part of that in the retina may have been free; in other tissues it was in the combined form as adenine-flavin dinucleotide or flavoprotein, neither of which is photolabile.

Although these results were clear-cut, they do not preclude the possibility that the conditions for the destruction of riboflavin or local lack of it may be quite different in the living eye. In the first place, although the authors state that the riboflavin was found to be in the combined form in tears, this determination was, perhaps, the least conclusive in excluding the presence of the free form, of

those they performed because of the difficulty in obtaining adequate samples of tears. Moreover, there are known to be two physiological types of stimulation of lachrymation and these might conceivably differ in regard to the concentration and form of riboflavin in the tears produced. From a theoretical standpoint, one would expect the lachrymal secretion to contain free riboflavin, inasmuch as two typical secretions, milk and urine, do so. The ox eyes tested with light for loss of riboflavin were not bathed in physiologically normal lachrymal secretion. Even the flavin within the eye tissue might be more vulnerable in living than in a lifeless specimen because many compounds are known to occur in quite low concentrations within the body at any given time due to the rapidity with which they are transformed in metabolism. In the case of riboflavin, the chance of destruction of the free form might exceed its apparent concentration in ocular tissues. Moreover, light and strain in the eye might conceivably initiate destructive metabolic processes in living tissue aside from a direct destruction by the light itself. In regard to the possibility of an unusual incidence of ocular signs among aviators or individuals with snowblindness, it might be conjecjectured that the light reflected from snow or clouds might be of a sufficiently different quality from ordinary light as to produce a somewhat specific effect on the eye.

However, the question as to whether the eye is rendered deficient in riboflavin through the action of light is only one small part of the larger problem which has been intensively debated, especially for the past two years, as to the identity of the specific signs of ariboflavinosis, the value of ocular manifestations in the early appraisal of riboflavin deficiency, and the actual frequency of occurrence of ariboflavinosis.

It is believed by some authorities that a lack of knowledge of the exact anatomy of the eye may have led to misconceptions and fallacies. The terms, "corneal vascularization" and "proliferation of the limbic plexus" have evidently been employed with various meanings. Gregory (20) points out that they have been used frequently to denote only an engorgement. The area actually referable to the limbus itself, he believes, is sometimes only vaguely defined; it should be recognized as denoting the whole zone where the sclera and cornea overlap like a watch glass in a groove, of variable width but averaging 1 mm. Vessels seen in this area may be inaccurately ascribed to the cornea. The concept of a "normal avascular zone" between the limbus and the cornea is thought by Vail and Ascher (21) to result from an incorrect interpretation of the facts. The fine vessels which occur normally in this zone are customarily empty of red corpuscles and are relatively invisible. However, Vail and Ascher consider that even the most distally situated of these limbal loops of the superficial marginal plexus contain a fluid, probably blood plasma or plasma diluted with aqueous humor. Even slight irritations may fill these previously invisible loops with red cells very quickly. Hence, the mere presence of filled vessels in transparent tissue is not a proof of "corneal vascularization." The authors believe that the term is merited only when real vascular proliferation, or the formation of entirely new blood vessels has taken place, as in corneal disease. They prefer to employ the terms "limbal hyperemia" and "concentric collaterals" to designate the engorged vessels of a preëxisting limbal plexus; here, the only proliferation which may take place is a multiplication of the cells of the engorged vessel walls to permit an increase in diameter.

Vail and Ascher distinguish between the extent and the intensity of the hyperemia of the limbal meshwork: They believe that the extent is conditioned by the duration of the disease; the intensity parallels the severity of the causative pathological process. In only long standing inflammation would they expect to find genuine vascular proliferation into corneal tissue proper beyond the most distal arcades. Gregory (20) also emphasizes the multiplicity of the agents capable of readily inducing a superficial circumcorneal injection: vigorous rubbing of the eye for a moment; exposure to wind, cold, bright light, mild chemical irritants; mild infections; injections of nicotinic acid; and numerous other causes.

The characteristics which are believed to mark off corneal vascularity due to a deficiency of riboflavin from corneal vascularity due to other causes are variously defined. The following opinions have been expressed in recent publications: Circumcorneal injection may be considered an early stigma of ariboflavinosis only when supported by other clinical findings (22); only the invasion of the clear cornea by capillaries of the limbus is likely to be of definite dietary origin, although some mild ariboflavinosis might be excluded by this standard (23); "this is always bilateral, though not always equally advanced in both eyes; it is always symmetrical—that is, it invades the whole circumference of the cornea in both eyes, although owing to the sclerocorneal 'overlap' in the segment of the cornea covered by the upper lid it is rarely conspicuous there; it forms a more or less regular pattern of very fine, streamerlike superficial vessels . . . Circumcorneal injection is frequently absent until a late stage, when deep vascularization and corneal opacities may appear . . ." (24). In addition to the objective records of ocular signs already mentioned (8) (21), another such record is the publication of photomicrographs of a human eye of a subject previously

diagnosed by the slit lamp as deficient in riboflavin. The eye was removed postmortem and injected with India ink (25).

The final criterion which distinguishes ocular, as well as other manifestations for which a deficiency of riboflavin is responsible, from other types of pathological signs is generally agreed to be the response to riboflavin doses carefully administered. Evidence from such tests, some of which are summarized below, is seen to be conflicting and confused. Attempts have also been made with, perhaps, even less success to correlate specific manifestations of deficiency with the food intake of the individuals in which the signs occur. Accurate dietary records are difficult to obtain at best, and, in the case of chronic deficiencies, the records must cover considerable periods of time in order to furnish any conclusive correlation with the development of manifestations. The expedient of questioning the patient about his dietary habits may yield approximations of some limited value, but those who have worked extensively in this field are conscious of the limitations of this method (26).

Pirie (27) has expressed regret that ophthalmologists are prone to ignore the findings of research and investigators to neglect detailed examinations of the eyes. The paper of Vail and Ascher (21) is of particular importance because the authors worked both in a department of ophthalmology and in a nutrition clinic over a period of three years. They examined the eyes of 711 patients; part of these were in the Birmingham Nutrition Clinic, part in the Outpatient Eye Clinic of the University of Cincinnati. Concentric collaterals were found in about an eighth of the Alabama patients and in over one half of those seen in Ohio. Subjective ocular symptoms and frank conjunctivitis were common but corneal vascularization was absent except in patients giving evidence of previous corneal disease. No correlation was found between the occurrence of concentric collaterals and quality of diet in 69 patients studied. The effect of riboflavin therapy was negative in the cases treated.

Machella (28), and Machella and McDonald (29) have presented evidence for their doubt of the validity of the so-called ariboflavinosis syndrome. They cite instances from the literature of failure of riboflavin therapy to relieve cheilosis, dermatitis, keratitis, or glossitis, and of evidence which they believe justifies their skepticism as to whether riboflavin was the active agent or some other feature of the treatment, where improvement was secured. From their own studies, they report negative results from the use of 6 mgm. or more of riboflavin for 4 to 180 days in the treatment of 28 subjects showing one or more manifestations ascribed to riboflavin deficiency, namely, 13 cases with cheilosis, 4 with pemphigus, 9 with corneal lesions, and 6 with typical glossitis. Even with the added use of hydrochloric acid no significant favorable response was secured in any subject except in those instances where pure riboflavin was replaced by some other therapeutic supplement such as brewer's yeast.

Goldsmith (30) had opportunity to observe the effect of riboflavin therapy on cases diagnosed as deficient in riboflavin. She appraised the nutritional status of 200 consecutively admitted patients in Charity Hospital in New Orleans; symptoms and physical signs were judged to give decisive evidence of ariboflavinosis in 44 patients (22 per cent). Slight corneal vascularization was common, responded little or not at all to riboflavin therapy and was not considered evidence of riboflavin lack. Administration of riboflavin was effective in rapidly clearing conjunctivitis and subjective ocular symptoms, more slowly with those lesions of lips, tongue and cornea which responded, and most slowly with certain skin lesions. Inadequacy of riboflavin was thought by Goldsmith to be the most frequent cause of deficiency disease in that locality.

From 658 urinary riboflavin determinations, Feder, Lewis and Alden (31) judged that the body's supply of riboflavin was more fairly reflected when the excretion was expressed as μg. per ml. than as μg. per hour of collection. An arbitrary assumption was made that, below an excretion of 0.3 μg. of riboflavin per ml. of urine, an individual was in a state of deficiency. On this basis, 25 per cent of a group of medical students were deficient, as were also 30 per cent of white draftees, 50 per cent of negro draftees, and 65 per cent of a rural population (vicinity of Atlanta).

Clarke and Prescott (32) reported 17 cases of vitamin B complex deficiency seen by them among patients with nervous disorders. Nearly all of them showed at least one of the signs originally considered specific for riboflavin deficiency. In only a few of these cases did the treatment consist in dosage with riboflavin alone; stomatitis was reported to respond in a short time and improvement continued for weeks. Duckworth's two cases of cutaneous and oral lesions healed on the administration of riboflavin (33) but therapy was not restricted to this.

Four hundred consecutive patients of the clinic and wards of the Stanford University Hospital were examined and judged in regard to nutritional and vitamin deficiencies (34). Approximately a fourth were judged to be taking a poor diet; 11.4 per cent of these gave evidence of clear-cut vitamin deficiency. Many of the cases had multiple deficiencies; two were judged definitely deficient in riboflavin and one mildly deficient.

Circumcorneal injection occurred in 34.3 per

cent of 204 unselected patients in the Edinborough Royal Infirmary (35), and in 68 per cent of those aged 50 or over; in 8 uncomplicated test cases the injections did not respond to riboflavin therapy but did do so in 5 of 8 patients who gave evidence of vitamin deficiency.

Six volunteers were secured for a riboflavin depletion study (36) from a group of students for whom a special diet table was provided by the student health service at the University of Minnesota. These six individuals were on a reducing regime and presumably restricted their food intake to the diet furnished at their special table, which provided 71 mgm. protein, 1300 Calories and 471 μg. of riboflavin daily for the five weeks of the experiments. Three of the subjects were given 3 mgm. of riboflavin in addition daily. It was in this control group that the only definite evidence of corneal vascularization occurred. Moreover, this failed to respond when 9 mgm. daily of riboflavin were given. One subject in the depletion group experienced severe photophobia which persisted until the normal diet was resumed. It might possibly be significant that these two were the only subjects who showed a decided loss of weight during the period, 12 and 8 pounds, respectively. They were, in all probability, in negative nitrogen balance. In an experiment on the influence of protein metabolism on riboflavin stores (37), 13 human subjects excreted a daily average of 1.45 mgm. of urinary riboflavin during a four-day fast, the magnitude of the excretion suggesting an origin chiefly in the liver. This is in harmony with earlier work on rats (38).

The question has been raised as to whether or not riboflavin therapy may be efficacious against manifestations, especially ocular ones, which do not result from riboflavin deficiency *per se*. Wolbach and Bessey (39) considered it possible that liberal riboflavin therapy might be of value in corneal injury of diverse causation. Conners, Eckardt and Johnson (40) found that rosacea keratitis, marginal corneal ulcers and catarrhal corneal infiltrates responded immediately to parenteral injection of riboflavin. On the other hand, only negative results were obtained by Fish (41, 24) in treating 10 cases of acne rosacea keratitis with riboflavin alone, whereas healing resulted in 30 individuals, including these 10, when routine treatment was given, with or without accompanying doses of riboflavin. Wise (42) also failed, except in one case, to relieve rosacea keratitis in 21 patients whom he treated with adequate doses of riboflavin. This discrepancy in results among these investigators has not been resolved but may rest, in part, on differences in diagnosing and classifying cases of a complicated disorder of unknown etiology, and, in part, on a difference in the prevalence of riboflavin deficiency in the areas represented by these investigators.

Not only ocular signs but cheilosis also has been questioned as a specific manifestation of riboflavin deficiency. Eight of Machella's patients who had no signs of deficiency except cheilosis failed to improve with riboflavin therapy (28). This was true also of 34 cases reported by Ellenberg and Pollack (43); 32 of these were edentulous, 1 had only 1 tooth remaining and 1 was a case of malocclusion. The corners of the mouths sagged into creases in which saliva tended to be retained and give rise to fungus growth. The cases responded to proper dental adjustment, not to riboflavin therapy. Nippert and McGinty (44) encountered a mixture of this type and true ariboflavinotic cheilosis in the same patient; both dental adjustment and flavin were necessary for cure.

Jeghers (45) has given an interesting physiological interpretation of the specificity of the two types of glossitis due to pellagra and to ariboflavinosis respectively.

A number of surveys of populations have been made for signs of riboflavin deficiency, with or without the collection of dietary records or tests with therapy.

Sanstead's 366 subjects (46) comprised children 7 to 18 years of age in a parochial school, National Youth Administration workers, and a group of adults. 80 to 95 per cent of these individuals had some degree of corneal invasion by capillaries. The children showed an incidence of 36 per cent of central penetration of the cornea with 2 or more tiers of capillary loops, whereas the incidence was 72 per cent among the N.Y.A. workers who probably were on a poorer economic level. The adult group, however, ranked higher than either of these groups in regard to incidence of severe stages (4 or more loops), the percentage being 5.8 as against 1.9 for the children and 3.7 for the youths. Fifty-two individuals received riboflavin therapy; 5 mgm. were given three times a day to the older groups for 60 days and twice a day to the children for 49 days. Each group had an appropriate control group to which no supplement was given. No significant improvement was observed; although fluctuations in the area and degree of involvement occurred during the study, this was not essentially different in the treated and control groups. Hence, Sandstead doubts whether such superficial vascularization of the cornea as he observed in this study should be regarded as a diagnostic sign of riboflavin deficiency.

Twenty-four women in a low income population group in Austin, Texas, (47) made collections of duplicates of their daily diet for analyses for periods of 1 week or more and were examined for anatomical evidence of vitamin deficiencies. The average intake of riboflavin was 0.68 mgm. per

1000 Calories or 0.78 mgm. total per day, ranging from 0.52 mgm. to 1.8 mgm.; the latter figure is the recommended daily allowance for a sedentary woman. The intake of 19 out of the 24 women fell between one fourth and one half of the recommended allowance. Cheilosis, corneal vascularity, or skin lesions, characteristic of ariboflavinosis, were found in 7 of the 15 subjects examined by Dr. Norman Jolliffe.

Gregory (20) examined 1059 supposedly normal people and found only a 3 per cent occurrence of corneal vascularization comparable with ariboflavinosis. Only about half of these had injection or even fullness of the limbic plexus and only a fourth showed other signs as glossitis or cheilosis.

Wilson (48) examined 3050 Oxfordshire children in 1939 and substantial proportions of these in two succeeding years. He found 11 cases of cheilosis the first year and 8 new cases in the two succeeding years.

One thousand one hundred and fifty-three aircraft workers in Southern California showed a high incidence (23 to 43 per cent) of subjective ocular symptoms. There was some degree of corneal vascularization in every case and streamer type arcades in 42.5 per cent; 9.3 per cent had 1 or more of other physical signs of riboflavin deficiency. Diet histories showed that most of the men were getting moderately good amounts of riboflavin (49).

Milam (50) found a mill community in North Carolina to have a riboflavin intake about one half of the standard recommended allowance.

In a nutrition survey carried out by Riggs and associates (51) on 260 boys and 286 girls in an urban suburb near Toronto, a comparison was made between the nutritional status of these children and their intake of riboflavin and other factors. The records of foods consumed for one week indicated that 43 per cent of the boys and 64 per cent of the girls ranked as excellent in their intake of riboflavin when this was compared with the recommended daily allowance approved by the Canadian Council on Nutrition. Physical examinations revealed no cases of cheilosis. No correlation was found between riboflavin intake and ocular manifestations. About a fifth of the group had intakes of riboflavin less than 70 per cent of the recommended allowance but practically none of these showed corneal vascularization. Most of the 7 per cent of the girls and 5 per cent of the boys who showed moderate or marked vascularization were found among the group whose dietary records indicated an excellent intake of riboflavin. Somewhat the same distribution between the groups held true for photophobia and lacrimation. The authors express doubt as to the value of the specific tests available at present for the detection of so-called subclinical states. This opinion seems to be shared by many others; it appears necessary to defer judgment for the present on the prevalence of riboflavin deficiency in the population at large. Various discussions, reviews and symposia on different aspects of the human requirement for riboflavin have appeared (20, 27, 52 to 63).

Experimentation on the requirements of animals for riboflavin has furnished a very valuable basis for searching for clinical manifestations of ariboflavinosis in man and for planning depletion studies with human subjects. Work with animals is perhaps a particularly desirable preliminary in the case of this vitamin, inasmuch as the period necessary for manifestations of depletion of human subjects may be more prolonged than for thiamine and ascorbic acid and severe clinical effects may possibly be less completely reversible.

There are, necessarily, problems inherent in the conversion of even well established quantitative results with animals to human requirements and recommended allowances because of such differences in the two types of subjects, as size, surface area, rate of metabolism, activity, types of intestinal flora and many other factors. However, the broad basis furnished by results with animals makes for economy in setting up experiments with human subjects.

It would be expected that the results of laboratory experiments with monkeys as representatives of primates would be particularly applicable to human requirements. It is of great interest, therefore, that a preliminary report has recently appeared (64) on the manifestations of riboflavin deficiency in the monkey. These included failure of growth, asthenia, incoördination of limbs, a specific type of dermatitis, and a sharp drop in hemoglobin and to a less extent in white blood cells, shortly after the appearance of the dermatitis. The dermatitis, of a peculiar "freckled" type appearing first as small red dry spots, later as extensive dark scabs, was distributed chiefly at sites of hair growth on the face and groin, and, in severe cases, in other areas. Biotin additions had no effect on the pathological signs. It was particularly notable that no cheilosis occurred nor were the eyes involved; although no histological sections or examinations with slit-lamp microscopy were reported, no vascularization of the cornea was seen grossly, even after 5 to 7 months maintenance on the ration low in riboflavin. It is well recognized that the results of acute deficiencies may differ from those of the mild chronic type.

The freckled dermatitis of the riboflavin deficient monkeys responded completely to sufficiently high doses of riboflavin, i.e., 100 to 500 μg. per day, in as short a time as 10 to 14 days. Smaller doses were effective in the milder cases. The anemia, however, persisted much more stubbornly. From these preliminary studies it is estimated by this laboratory (65) that an adult monkey can be main-

tained on an allowance of 15 to 20 μg. of riboflavin per kilogram of body weight and a rapidly growing monkey on about double this dosage. This is of the same order of magnitude as the requirement of the dog for riboflavin. A recent report (66) showed that an adult dog of 10 kgm. or over could be maintained on 15 μg. of riboflavin per kilogram of body weight and that 30 μg. per kilo was a mimimum level for good growth in young dogs. That this standard is less than the previously reported one (67) of 50 to 60 μg. per kilo for growing dogs probably is accounted for by the different sizes of the animals and by the relative distribution of the total intake of riboflavin in the ration, in the pure synthetic form and in a liver extract, with the possibility of resulting differences in absorption, excretion and intestinal synthesis (68). Taking these factors into consideration, the probable requirements might be estimated as 25 μg. per kilo for the adult dog and 40 for the growing dog (65).

The needs of two types of rats for riboflavin and thiamine have been compared (69). The white rat was found to require 80 to 150 μg. of thiamine per 100 gram of synthetic ration, the cotton rat circa 150; the white rat 100 to 150 μg. of riboflavin, the cotton rat more than 80 and less than 300 μg.

Long-continued experiments in Sherman's laboratory have demonstrated that the total results of mild deficiencies of riboflavin are not necessarily quickly apparent (70). The effect of liberal levels of riboflavin intake in increasing the nutritional well-being of rats was not clearly appreciable in the first generation but became apparent through successive generations maintained on the diets. Adult vitality and length of life were satisfactorily supported by 3 μg. of riboflavin per gm. of air-dry food mixture; however, more favorable growth of the offspring and ability to tolerate subsequent low levels of riboflavin and of thiamine were conferred by a threefold higher riboflavin intake.

During some experiments on blood regeneration in dogs, a delicate test of riboflavin deficiency was discovered (66) which was observable among the earliest of those characteristic manifestations which occurred during the riboflavin depletion. Whereas a pure synthetic diet supplemented with a full quota of crystalline B vitamins was adequate for supporting hemoglobin regeneration during long periods of bleeding, it became inadequate for this purpose when riboflavin was omitted from the supplements, thus producing an uncomplicated deficiency for this factor. Competition of growth for the riboflavin available made the regeneration of hemoglobin a more serious problem in growing dogs than in adult.

Thus, again, accent is given to the protection which an adequate intake of riboflavin affords in such emergencies as loss of blood.

An even more spectacular demonstration of latent injury due to riboflavin lack has been furnished by some remarkable experiments on congenital defects. Striking malformations in newborn rats produced by mothers on a deficient diet of corn meal, wheat gluten, viosterol and inorganic salts, and preventable by small additions of dried pig liver, were reported in 1942 by Warkany and Nelson (71, 72). Later, the use of a purified diet with additions of members of the vitamin B complex in synthetic form, led to the discovery that the absence of riboflavin had been responsible for this peculiar abnormality (73). The malformations included the shortness of certain bones, the fusion of others, supernumerary digits and cleft palate.

Thus, a dietary lack of riboflavin not complete enough to seriously repress growth and reproduction nor to produce noticeable manifestations in the first generation, nevertheless, interfered with the normal development of embryonic tissues. This demonstration gives grounds for hesitancy in accepting short adult human depletion experiments as the sole basis for recommendations for allowances of nutritive factors for long-continued use by heterogeneous populations. The conclusion may be accepted that "further evidence is needed before any level can be established" (60).

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THE THIAMINE REQUIREMENT OF MAN

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An accurate knowledge of human thiamine requirements is a very pertinent matter at the present time. The physician wishes to know when to prescribe thiamine, the home economist is concerned about the need of supplementing conventional diets with vitamin preparations and the food manufacturer seeks light on the question of whether or not to reinforce his food products. Without such accurate knowledge governmental agencies find it difficult to make wise decisions on many questions affecting the public welfare—the problem of proper labelling of foods and drugs, the even more vital matters of food rationing and food export to war-torn countries. From the point of view of the national economy the question as to whether the present enormous annual expenditure for B vitamins is justified or whether the public would not be better served by diverting this outlay into other channels, is one that demands an answer. An exact answer to these questions cannot be given at the present time, for the gaps in our knowledge are still wide. To point out these gaps

and to define the applicability of such data as is now available will be the task of the present review.

The present discussion will be limited to a consideration of the *minimum thiamine intake required for the maintenance of health*—a question of fact. How much of a margin of safety should be allowed beyond this is a matter of individual opinion.

Two types of data are available for determining minimum requirements: studies of the intake required to protect individuals from deficiency, as manifested by accepted symptoms and laboratory criteria, and studies of the intake required to abolish such manifestations. The prophylactic experiments are likely to place the requirement slightly on the low side because of their limited duration which does not exclude the possibility that symptoms might have developed in a longer time. They are, however, far more accurate than therapeutic studies in which an unnecessarily high dosage is invariably given. For this reason only the prophylactic studies will be considered here.

Although it is clearly appreciated that the thiamine requirement is affected by the composition of the diet as well as by other factors which are discussed below, we shall follow the convenient practice of expressing thiamine requirements in terms of milligrams per 1000 calories.

The thiamine requirement of the normal adult. The first direct observations on this point are those of Jansen in 1932 who assayed the diets of Javanese laborers. According to his estimates, (1) a diet containing 200 units (0.6 mgm.) per day was sufficient to protect against beriberi. A slightly higher figure for the normal Javanese dietary is given in a subsequent report by Van Veen, (2) who places the daily intake between 0.6 and 1.0 mgm. per day. Since the caloric intake of this group is usually between 2200 and 2500 calories, it appears that a thiamine intake between 0.24 and 0.44 mgm. per 1000 calories will protect them against deficiency. These observations from the Netherlands Indies are of particular interest as contrasted with more recent experimental studies in this country. It is noteworthy that the protection obtained was permanent. The high proportion of carbohydrate in the Javanese diet was a factor unfavorable to a low thiamine requirement. On the other hand the diet was a monotonous one, a factor somewhat favorable to a low requirement.

Since 1936 a number of studies have been reported in the American and English literature in which volunteers have taken diets deficient in thiamine for variable lengths of time. In some of these, indubitable evidences of thiamine deficiency developed and were abolished by the administration of thiamine; in others the development of thiamine deficiency is highly questionable. The studies of Alvarez et al (3) failed to yield impressive evidence of thiamine deficiency. The restriction of thiamine in their experimental diets was only moderate and the manifestations they observed—anemia, abnormalities of gastric secretion—do not conform to the picture of thiamin deficiency as generally recognized. Jolliffe and his collaborators (4) reported the development of thiamine deficiency in a group of hospital internes who ingested a low thiamine diet; the manifestations of deficiency developed within a few days and responded promptly to the administration of thiamine. Doubt has been cast on the validity of these observations by subsequent workers who have found that a far longer time was required to produce symptoms. Wang and Yudkin (5) in experiments on a thiamine deficient diet obtained symptoms within the first two weeks—constipation, lassitude, anorexia and fatigue—but they concluded that these could not be attributed to thiamine deficiency since they were not abolished by a thiamine supplement. Shils, Day and McCollum (6) obtained no symptoms or elevation of bisulphite-binding substances in the blood in the course of 38 days on a diet containing between 0.15 and 0.18 mgm. of thiamine per day, and Najjar and Holt (7) in a single experiment lasting 40 days observed no symptoms on a diet completely devoid of thiamine. Robinson, Melnick and Field (8) gave a single subject a diet containing 0.267 mgm. per day, and between the 12th and 22nd days observed the development of pain and tenderness in the calf muscles, paresthesias and dyspnea on exertion, symptoms which responded to a supplement of crystalline thiamine. However, these workers were unable to demonstrate a rise in bisulfite-binding substances in the blood of their subject, nor any reduction of this value following the administration of the supplement.

During the past few years extensive studies of experimental thiamine deficiency have been carried out by 4 groups of investigators: by Williams and his collaborators (9) from the Mayo Clinic, by Elsom et al. (10) at the Philadelphia General Hospital, by Keys and his collaborators (11) in Minneapolis and by Najjar and Holt (12) in Baltimore. In a series of well conceived and well executed experiments carried out upon inmates of a psychiatric hospital the Rochester investigators studied the effect of diets containing different levels of thiamine for prolonged periods of time and made observations upon symptoms, thiamine excretion and blood pyruvic acid. They concluded (9f) that an intake of 0.45 mgm. per 1000 calories was not quite adequate to prevent symptoms and biochemical changes of deficiency, and that the minimum requirement must be slightly above this figure. Elsom and her collaborators, who likewise carried out long term experiments on carefully analyzed diets, found that a somewhat lower intake—0.35 mgm. per 1000 calories—prevented symptoms. In the Minneapolis

studies an intake of 0.23 mgm. per 1000 calories was found to be compatible with health, and even lower figures were found in the study of Najjar and Holt (0.15 mgm. per 1000 calories). These differences in requirement are not irreconcilable. In part they may be attributed to differences in experimental conditions, in part to differences in interpretation.

In the opinion of the reviewer the clinical and laboratory criteria accepted by the Rochester investigators as evidence of thiamine deficiency have not been sufficiently rigorous. Much stress is laid by them upon a group of neurasthenic symptoms which appeared upon the experimental diet and were interpreted as evidence of thiamine deficiency. The difficulties in evaluating such symptoms are obvious and are admitted by these investigators themselves. The possibility that psychological factors related to the experiment may have played a part in the production of these symptoms is very difficult to exclude. It is also worthy of note that in some of the Rochester experiments at least (9d), an anemia developed on the experimental diet. This finding, which is not a part of the recognized picture of thiamine deficiency, may well explain some of the symptoms noted. It is germane to point out that similar neurasthenic symptoms have been observed in the experiments of others (3, 4, 5) under circumstances where conditions were such as to preclude the development of thiamine deficiency. Although the reviewer is prepared to admit the fact that thiamine deficiency may produce neurasthenic symptoms, he believes that their frequency and value as an early sign of thiamine deficiency have been greatly overstressed. It is of interest that physicians of the Netherlands Indies who see a great deal of beriberi and are constantly on the watch for its first manifestations fail to encounter the picture of "subclinical thiamine deficiency" and are astonished (13) by the long list of symptoms ascribed to it by physicians in the United States. Although the reviewer takes exception to some of the clinical evidence of thiamin deficiency in the Mayo Clinic experiments, he is fully prepared to agree that in other experiments symptoms and signs of deficiency were unquestionably present—those which were characterized as "advanced" rather than mild deficiency. In every instance, however, the subjects developing such unquestionable symptoms were on intakes which did not exceed 0.22 mgm. per 1000 calories.

Turning to the laboratory criteria, the reviewer feels that the excretion of less than 100 γ thiamine in the urine in the 4-hour period after a parenteral injection of 1 mgm. thiamine is not *per se* an evidenceof thiamine deficiency. Williams and his coworkers state that the excretion of less than 100 γ has been regularly associated with a "considerable degree" of thiamine deficiency whereas an excretion below 50 γ has been associated with severe deficiency. The reviewer believes that the latter value is probably closer to the borderline of real deficiency. In the experiments of Najjar and Holt symptoms attributable to thiamine deficiency were never observed until the excretion with a load test had fallen below 60 γ in 4 hours and not with any regularity until it had fallen below 50 γ. In the Rochester data only subjects on an intake as low as 0.22 mgm. per 1000 calories exhibdite load excretions as low as 62 γ in 4 hours.

Data on blood pyruvate are notoriously difficult to evaluate, because of the fact that this metabolite is readily elevated by exercise and excitement, conditions which obtain not infrequently in psychiatric patients and in many normal patients in association with venepunctures. Although the post-dextrose elevation of blood pyruvate in many of the Mayo Clinic experiments is of such magnitude as to dispel reasonable doubt on this score, there are other instances in which interpretations have been made from lesser rises, the significance of which may be questioned. Although some of the subjects on a thiamine intake of 0.22 mgm. per 1000 calories developed blood pyruvate values above 2 mgm. per 100 cc. after the administration of dextrose, it is to be noted that none of the subjects receiving 0.45 mgm. per 1000 calories did so. The reviewer believes that the Mayo Clinic data may be interpreted as indicating a minimum thiamine requirement barely in excess of 0.22 mgm. rather than barely in excess of 0.45 mgm. per 1000 calories.

In the experiments of Elsom and her collaborators, four subjects were observed with "definite" evidences of deficiency. Two of these (subjects D. C. and E. V.) who had received a daily intake of 0.2 mgm. thiamine per day showed an improvement after thiamine therapy that was impressive and there is little ground for questioning the diagnosis of deficiency. In subject R. A., whose intake was 0.353 mgm. per day, it is probable, too, that the symptoms observed were due to thiamine deficiency, although it is to be noted that irritability, muscle tenderness and edema failed to respond to thiamine alone, clearing up later when a B complex supplement was added. The fourth patient (I. C.) however, must be excluded from a study of the normal thiamine requirement, since this subject developed symptoms following a severe intercurrent infection and the response to a thiamine supplement continued for 38 days was far from satisfactory. Although some of the observed symptoms showed improvement, muscle tenderness persisted and edema was even increased during the period of supplementation. The reports of Elsom et al. do not contain detailed information about the patients who developed symptoms of "early deficiency," but it is to be noted that

none of these individuals was found (10d) to have any elevation of the blood pyruvate or any alteration of the lactate/pyruvate ratio. Judging from the patients who developed definite deficiency, the data of these investigators indicates the minimum thiamine requirement to be somewhat in excess of 0.353 mgm. per day (0.17 mgm. per 1000 calories).

The excellent study of Keys et al. (11), although designed primarily to test the effect of work on the thiamin requirement, is of very pertinent interest here, since it showed that even under conditions of physical stress a thiamine intake of only 0.23 mgm. per 1000 calories was sufficient to protect men from symptoms of deficiency for 10 to 12 weeks at least.

The study of Najjar and Holt differed from the foregoing in the fact that depletion was carried out very gradually over a period extending as a rule over 18 months. It differed also in the fact that a synthetic diet was used throughout which was not varied from meal to meal or from day to day. This diet consisted of vitamin-free casein, crisco, dextrimaltose, a mineral mixture and a vitamin mixture, the only variable of which was the thiamine content. The basal diet contained a small amount of thiamine in the dextrimaltose, the thiamine content of which was found to be 72 γ per 100 grams. From this source the subjects obtained. 128 mg. per 1000 calories. In addition to this they received thiamin in their vitamin mixture in quantities of 0.5 mgm. per 1000 calories at the start of the study which were gradually decreased to zero. For several months prior to the final removal of the thiamine supplement, nine subjects subsisted on a total thiamine intake of 0.178 to 0.198 mgm. per 1000 calories without developing any evidences of deficiency. When the supplement was removed and only the basal diet containing 0.128 mgm. per 1000 calories was given, unmistakable deficiency symptoms appeared within a period of 3 weeks to 3 months in 8 out of 9 subjects. Urinary excretions of thiamine had been at minimal levels for many months prior to the last decrease in thiamine intake and showed no further drop at the time of the development of symptoms. Thiamine load tests (in which the 4 hour excretion of thiamine in the urine was measured after an intravenous injection of 1 mgm.) showed a drop preceding and associated with the development of symptoms. Prior to the development of symptoms the 4-hour excretion fell below 100 micrograms and at the time of the development of symptoms values below 53 micrograms were obtained in every instance. Only once was a value below 50 obtained in a subject without symptoms of deficiency. The excretion figures given by these deficient subjects are thus in close agreement with those obtained by Williams et al. in patients with unquestionable deficiency symptoms.

The Baltimore experiments would place the minimum thiamine requirement between 0.128 and 0.178 microgram per 1000 calories, somewhat lower than that obtained in the 2 other experimental studies. On the other hand, it is reasonable to expect that requirements would be lower on a diet which is constant—meal after meal—both in respect to calorigenic foods and thiamine content—than on a diet which may at times provide an excess and at other times a deficiency of thiamine.

It seems justifiable to conclude that with a constant diet the minimum requirement of adult man lies at a point somewhere between 0.13 and 0.17 mgm. per 1000 calories, whereas with a diet constructed from natural foods in which there is some variation both in the food and the thiamine intake, the minimum lies between 0.17 and 0.23 mgm. per 1000 calories. The observations in Java indicate that intakes of the order of magnitude of 0.24 and 0.44 mgm. per 1000 calories will protect against thiamine deficiency for an indefinite period of time.

The thiamine requirement of the infant. The most illuminating information about the minimum requirement of the infant is obtained from observations of infants fed on breast milk, a food which is known to be low in thiamine (15–24). According to the latest analyses of Knott (24) breast milk averages about 15 micrograms per 100 cc. and under ideal conditions of maternal diet about 20 γ per 100 cc. It may at times be increased above 30 γ by supplementation of the mother's diet or, when the diet is substandard, may fall below 10 γ per 100 cc. It is known from observations in the Orient (14) that the thiamine content of breast milk may fall so low as to produce beriberi in the infant, but no exact information is available as to how low this level is. The Australian workers Slater and Rial (21) and Clements (25) present clinical evidence that symptoms of thiamine deficiency—failure to gain weight, constipation and vomiting—may occur when the thiamine concentration of breast milk falls below 11 or 12 γ per 100 cc. The writer does not find their data convincing on this point. The specificity of the symptoms may be questioned, and their data included instances in which a milk containing as little as 8 γ per 100 cc. produced no untoward symptoms. Widenbauer and Heckler (18) and Knott and her collaborators (24) fail to mention untoward symptoms in the infants whose mothers were secreting a milk containing less than 10 γ per 100 cc. and Morgan and Haynes (19) specifically mention the excellent health and normal weight gain of an infant whose mother's milk contained only 11 γ per 100 cc. Moreover, the relative frequency with which such low values

are encountered makes it seem improbable that such milk supplies less than the minimum thiamine requirement. Assuming a caloric content of 0.67 cal. per cc, a milk containing 10 γ thiamine per 100 cc. would furnish 0.15 mgm. thiamine per 1000 calories.

The question has been raised as to how the breast fed infant gets along on a thiamine intake distinctly less than that of the artificially fed infant. German writers (26) have maintained that breast milk favors the biosynthesis of thiamine by intestinal bacteria, a view based upon the observations of Reichelt (27) who reported that bacillus bifidus, a conspicuous member of the intestinal flora of the breast fed infant, was an excellent thiamine producer, surpassing yeast and the colon bacillus in that respect. However, Widenbauer and Kruger (28) found the thiamine content of the stools of the breast fed infant no higher than that of the artificially fed, and Knott and her collaborators (29) report lower urinary thiamine excretions in breast fed than in artificially fed infants, findings which speak against that explanation. In the opinion of the reviewer the relatively low apparent requirement for thiamine of the breast fed infant (0.15 mgm. per 1000 calories) may be attributed to the fact that his dietary is constant from meal to meal. He is thus comparable to the experimental subjects of Najjar and Holt (12) who, it may be recalled, were also able to get along on 0.15 mgm. per 1000 calories.

The attempt to draw deductions about the thiamine requirement of infants from urinary excretion data, as has been done by several investigators (30), is a highly questionable procedure, in view of our lack of standards based on known cases of deficiency.

Little can be said of the minimum requirement of older children. The studies of Knott et al., (31) Robb et al. (32) and Benson et al. (33) indicate levels of intake compatible with health, but do not reveal how far these are from the minimum requirement. Since the requirement of the infant under comparable conditions seems to be similar to that of the adult in terms of calories, it is to be expected that that of the older child will not differ greatly from it.

Physiological factors affecting the thiamine requirement. Pregnancy. There can be no doubt that thiamine requirements are increased during pregnancy, but exact data on the minimal requirement are not available. Since the growth of the young infant seems to demand no more thiamine per calorie than is needed for the maintenance of the adult, it is reasonable to suppose that the requirement of thiamine per 1000 calories will be the same as in the non-pregnant adult. Additional calories must, however, be provided to meet the needs of pregnancy.

Lactation. A similar lack of exact information is available about the thiamine requirements in lactation. It would seem certain that the minimum thiamine requirement of the nursing infant should be added to that of the mother, but whether more thiamine than this is required will have to await exact studies.

Exercise. The literature on the relation between thiamine and work performance has recently been reviewed (34, 35) and little can be added at the present time. Interesting studies carried out under the auspices of the Harvard Fatigue Laboratory (36, 37) suggest that exercise produces an acute demand for thiamine, and for some other component found in yeast. The experiments have, however, been criticised by Keys et al. (47) on several grounds. The laboratory evidence of thiamine deficiency was obtained by the questionably accurate thiochrome method of Egaña and Meiklejohn (38), and the clinical evidence of deficiency was meagre and for the most part subjective. Subjects receiving a concealed thiamine supplement showed almost as much deterioration in work performance as did the unsupplemented subjects, both groups showing improvement when, with their knowledge, yeast was supplied. The psychological factors in the experiment are thus difficult to evaluate.

Barborka, Foltz and Ivy (39), using trained subjects, observed symptoms suggestive of thiamine deficiency and impaired work output on a diet deficient in B complex which contained as little as 0.65 mgm. thiamine per day. They, too, obtained a favorable response to the administration of yeast. It may be noted, however, that their deficient periods occurred during the hot summer months, a factor which may have influenced symptoms and performance. It is not clear from the data presented that more than one subject showed the work deterioration described. The substitution of carbohydrate for much of the fat of their diet failed to exercise a deleterious effect, as might be expected with thiamine deficient subjects and, finally, the improved work output on yeast was not sustained.

More convincing to the reviewer are the studies of Keys and his collaborators (11). These investigators in a series of meticulous experiments, continued for 70 to 84 days, were unable to demonstrate any evidence of deficiency or of impaired physical performance in subjects whose thiamine intake was restricted to 0.23 mgm. per 1000 calories. It seems justifiable to conclude that exercise, although causing an increase in total caloric requirement and in the absolute requirement for thiamine, does not cause any increase in the requirement per calorie.

Closely related to the question as to whether exercise creates an additional demand for thiamine, resulting in *inferior* work performance if this is not met, is the question whether *superior* performance

can be obtained by increasing the thiamine intake well above levels that will protect against symptoms. Keys and Henschel (40) failed to find evidence of superior performance from supplements to U. S. Army rations and Bransby et al. (41) obtained similar results with industrial workers in England.

Learning. Claims have been made, notably by Harrell (51), that a thiamine supplement improves the learning capacity of children. Before such an important conclusion can be accepted it would seem to the reviewer that further work should be done; in particular, the effect of reversing the thiamine and the control group should be tried.

Climate. This subject has recently been reviewed by Taylor (42). It appears that the observations of Mills (43), whose studies on rats indicated a markedly higher thiamine requirement in hot weather, are not applicable to man. Losses of thiamine in the sweat are negligible, not exceeding 50 γ per day at the most, and there is some reason for believing that the unconscious economy of effort which occurs in hot weather (44) may more than compensate for this. Unpublished studies with which the writer is familiar have failed to indicate any need for an increased thiamine requirement under other adverse climatic conditions—high humidity, extreme cold or diminished oxygen tension.

Thiamine requirements in disease. It is obvious that no generalizations can be made here, for processes of disease vary in severity, but, quite apart from deficiency states which call for thiamine therapy, it may be well to recall the types of disturbance that lead to an increased demand for thiamine and may be regarded as indications for its prophylactic administration: (a) digestive disturbances of all kinds, which interfere with the absorption of thiamine; (b) circulatory disturbances, such as post-hemorrhagic shock (45) which interfere with the distribution of thiamine to the tissues; (c) conditions which increase the basal metabolism—fever and hyperthyroidism. The administration of thiamin is also indicated when the normal foods which supply it are restricted, or omitted, notably when patients are fed for any length of time parenterally. An interesting cause of thiamin deficiency in animals is the eating of certain raw fish which contain an enzyme that destroys thiamine (48, 49, 50). A similar cause of thiamine deficiency in man has not as yet been described.

Other factors affecting the thiamine requirement. It should be emphasized that although thiamine requirements are conventionally expressed in terms of calories of food consumed, this practice involves certain inaccuracies. Animal studies (46) indicate that, other things being equal, the requirement varies with the total calories metabolized, but it is not known whether a simple thiamine/calorie ratio holds for all levels of requirement. It may well be that the actively exercising individual who requires 5000 to 6000 calories per day needs relatively less thiamine per calorie than the sedentary individual. The effect of ingestion of an excess of food beyond the metabolic requirement is another matter that has not been clearly evaluated. Finally, it is known that the requirement for thiamine is reduced when fat forms a substantial part of the diet, and is probably greater for carbohydrate than for protein food. Although on theoretical grounds it would be preferable to express requirements in terms of metabolic requirements and to take into consideration the quantity and the proportion of the different foodstuffs in the diet, it is scarcely practicable to do this.

A further reason for not insisting on such refinements is the fact that marked differences exist in the thiamine requirement of individuals, differences which are far greater than those caused by variations in metabolic requirements. Elsom and her collaborators (10c) were impressed with the fact that the requirements of their experimental subjects did not seem to bear any close relation to the body weight and similar observations were made by Najjar and Holt (12, 42). It is conceivable that differences in the vitamin stores prior to the onset of the deficiency study might explain these discrepancies. That does not, however, seem to be an adequate explanation, for in the Baltimore studies the intake was reduced so very gradually and over such a long period of time that it is difficult to imagine that the initial store played much part in the picture. At least one important cause for the difference in individual requirements was discovered by Najjar and Holt (12) who observed that some of their experimental subjects who failed to develop symptoms promptly on their lowest level of thiamine intake were synthesizing thiamine in the intestinal tract, as shown by the fact that the daily excretion in the stools was greater than the intake. A striking correlation was obtained between the absence of symptoms and the quantity of free thiamine found in the stools. The quantity of thiamine so found was, however, insufficient to protect these subjects indefinitely under the conditions of the experiment, for eventually all but one subject developed thiamine deficiency.

The question as to the importance of biosynthesis as a factor protecting the individual against thiamine deficiency cannot be answered until further studies of this phenomenon are made. Evidence obtained from preliminary unpublished observations suggests that the composition of the diet is an important factor controlling biosynthesis. This cannot, however, be the only variable

since marked differences in biosynthesis were observed in individuals on the same diet.

SUMMARY. 1. The thiamine requirement is affected by the uniformity of the diet; the more uniform the diet the lesser the requirement.

2. The available evidence indicates that on a constant diet the minimum requirement for the normal adult lies between 0.13 and 0.17 mgm. per 1000 calories, whereas on a diet chosen naturally it lies between 0.17 and 0.23 mgm. per 1000 calories. A range of intake between 0.24 and 0.44 mgm. per 1000 calories appears to be protective against thiamine deficiency.

3. These same values appear to be valid for all age groups and for pregnant women and men undergoing strenuous exercise as well. In pathological conditions the requirements may be considerably increased.

4. The current practice of expressing thiamine requirements in terms of milligrams per 1000 calories consumed is probably the most practical procedure at the present time, although it is open to certain theoretical objections which are discussed.

5. It is pointed out that there are variations in the thiamine requirements of individuals, one important cause of which is the degree of synthesis of thiamine by the intestinal bacteria. Further studies are needed to evaluate this phenomenon.

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SOME ASPECTS OF VITAMIN C METABOLISM

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Within the past few years many investigators in the field of nutrition have emphasized the difference in effect on the body of a mild vitamin deficiency lasting over a considerable period of time, as compared with that of a more severe deficiency of but short duration. Since frequently the pathologic state thus induced is more severe in the former case, and requires a longer period for recovery, the importance of maintaining in the dietary adequate amounts of all essential nutrients is apparent.

Food sources. Recent reviews (1, 2, 3, 4, 5, 6) have shown a considerable percentage of industrial and rural populations with definite signs of deficiency of one or more vitamins or other nutrients which are directly traceable to dietary inadequacies. In many instances the omission of adequate sources of vitamin C or the improper handling of foods reduces the dietary intake of this vitamin to a dangerous degree.

While citrus fruits hold a place of pre-eminence in our diet as a source of ascorbic acid, the use of tomatoes probably can be considered the second most readily available source. A field grown vine ripened tomato may contain as much as 25 mgm. ascorbic acid (7). The use of tomatoes canned at the peak of the season frequently provides a food of higher ascorbic acid content than market available fruit in off seasons. Holmes, Jones and Richie (8) analyzed thirteen lots of late winter tomatoes and found an ascorbic acid content ranging from 2.5 to 22.0 mgm. per 100 grams of fruit. The average value of all lots was 8.8 mgm. per 100 grams. Tomatoes, canned at the height of the previous season gave an average ascorbic acid content of 14 to 15 mgm. per 100 grams. Ripe peaches (9), depending upon the variety, contain 3.84 to 12.86 mgm. ascorbic acid per 100 grams of fruit with the highest concentration directly under the skin. Varietal differences in ascorbic acid content are also found in red raspberries (10) and in new rather than in old potatoes (11). In some varieties of cabbage the ascorbic acid content decreases as the cabbage matures (12). Peppers on the other hand are an excellent source of vitamin C at all stages of ripeness, being highest when partially ripened, according to Lantz (13). He also found that the ascorbic acid content increases as the season advances. One variety, College no. 9, increased from 209 to 375 mgm. per 100 grams from August to November.

Methods of food preservation vary in their influence on the ascorbic acid content of the product. Canning has the advantage from the standpoint of the length of time the material will keep (14). Refrigeration is for short time preservation. Losses during drying and dehydration vary both with the method and material. Floyd and Fraps (15) have made a study of losses in ascorbic acid content in the commercial canning of Texas grapefruit juice. Tree ripened fruit, first grade, produces juice from 38 to 46 mgm. ascorbic acid per 100 grams. Canned fruit juices contained about 18.2 per cent less ascorbic acid than fresh juice. The inclusion of culls reduces the ascorbic acid content of the juice; with 10 per cent or less culls, the juice averaged 36.1 mgm. per 100 grams, while juice from 90 per cent culls contains but 29.5 mgm. ascorbic acid per 100 grams. Oxidative losses are low if pasteurization follows promptly after extraction (3½ minutes lapse, 6 per cent loss; 30 minutes lapse, 34.7 per cent loss). Of the methods of extraction of the juice (screws, burr press, rollers, graters) the screw extraction and burr (similar to domestic juice extractors) causes the greater destruction of ascorbic acid. Recent work in other laboratories indicates these processing losses to be rather high. Retention values of 98 to 99 per cent have been reported.* The loss of ascorbic acid in fruits and vegetables following maceration, as in the preparation of salad, may be appreciably decreased, according to McCay and Pijoan (16), by cutting or mincing with a plastic knife instead of one of metal.

The harvesting of leafy vegetables in the coolest part of the day (17), and packing of vegetables in crushed ice as soon as harvested and during transportation was found by Zepplin and Elvehjem (18) to decrease loss of vitamin C. Ascorbic acid was destroyed quite rapidly in spinach, chard, lettuce, and broccoli at room temperatures of 20 to 23°C; storage in a refrigerator favored its retention.

Blanching of vegetables preliminary to drying according to von Loeseche (17) aids in the preservation of vitamins, expels part of the contained oxygen and decreases the bacterial population. Blanching by steam at atmospheric pressures reduces the loss of mineral salts and vitamins as compared with hot water blanching. von Loeseche

*Personal communication from Dr. C. A. Elvehjem.

quotes the following figures from Chance as to loss of vitamin C by the two respective methods:

VEGETABLE	LOSS STEAM	LOSS HOT WATER
	per cent	*per cent*
Kale	19.7	43.6
Beets	14.8	36.6
Potato (white)	22.5	37.5
Cabbage	14.1	51.5

In a study of vitamin losses during dehydration and storage, Tressler, Moyer and Wheeler (19) found potatoes to retain but a trace of ascorbic acid. Beets lost one-third of their original content. Water blanching and dehydration of rutabagas caused an 85 per cent loss. Cabbage however, showed only 20 per cent loss of ascorbic acid during dehydration with practically no additional loss during storage at −40°F for three months.

Vitamin loss in large scale food preparation in defense plants and civilian cafeterias have recently been shown to be excessive. Heller, McCay and Lyon (20) found a 27 to 90 per cent loss in the ascorbic content of vegetables served in a cafeteria feeding 2500 people. Losses of other vitamins, while less were still high (thiamin 16 to 64 per cent, niacin, 2 to 61 per cent, and riboflavin 22 to 45 per cent). Similar results were obtained by Daum, Aimone and Hollister (21), who furthermore observed a greater loss of ascorbic acid to occur during the holding of vegetables for one hour on the steam table than resulted from cooking. Suggested remedies included a decrease in cooking and holding time, staggered preparation of foods, a more limited choice of vegetables and a preview of the menu. The use of whole boiled (22) potatoes instead of mashed conserves their vitamin C content even when held at steam table temperatures. Small amounts of sodium bicarbonate may be added in cooking fresh or tunnel frozen peas without causing additional loss of vitamin C (23). The cooking time is shortened, and unless the membrane surrounding the pea is broken as in plate freezing, only moderate losses occur by leaching into the cooking water. The uncontrolled adoption of this practice in the home is not be be recommended.

An unusual high source of vitamin C is rosehips, 100 grams of which contain 1200 to 1500 mgm. ascorbic acid.

Methods of analysis. The older methods for estimating the ascorbic acid content of urine, plasma, whole blood and its cellular constituents have been reviewed by Bessey (25) and later briefly by Ralli and Sherry (26). A critical study of the photometric methods of Mindlin and Butler (27) have been made (28, 29).

Technics for the determination of ascorbic acid in the presence of highly colored solutions, such as fruit extracts, have been developed for the Evelyn Photoelectric colorimeter by Bessey (30) and a potentiometric method by Harris and Olliver (31).

Aside from the handicap of colored solutions in titration procedures, various indophenol reducing substances other than ascorbic acid are encountered in the urine, feces, plant extracts, cereal products, milk powders and carmelized or fermented products. In a recent issue of Nutrition Reviews (32) it is stated that aside from ascorbic acid, 2:6 dichlorophenolindophenol will be nonspecifically reduced by such substances as stanous and ferrous salts, sulfites, sulfhydrol compounds, sulphides, thiosulfates, reductinic acid and "reductones" (formed by splitting of sugars by heat or fermentation). According to Enders (32), reductones are formed when sugars are heated at a suitable pH and especially in the presence of protein. These substances are suspected of having a structure somewhat similar to ascorbic acid with an aldol type of condensation between carbohydrate and protein derivatives.

Methods have been proposed by Lugg (33), Mapson (34) and Snow and Zilva (35) based upon the differential rates of combination of ascorbic acid and other indophenol reducing substances with formaldehyde at pH 1.5 to pH 2. At this acidity "reductones" condense but slowly with formaldehyde. Ascorbic acid is determined by difference in titration for total indophenol reducing substances and the value obtained for "reductones" by extrapolation from a series of determinations made at stated intervals. This method does not distinguish between l-ascorbic acid and close analogues (d-glucoascorbic acid, d-araboascrobic acid, etc.). It has also been suggested (36) that ascorbic acid may be titrated by 2:6 dichlorophenolindophenol in presence of "reductones" if the reductones are estimated at high acidity (20 per cent HCl); total reduction (reductones and ascorbic acid) being estimated after dilution with water to appropriate acidity.

It remains for future work to determine if these proposed methods are superior to existing photometric methods (30) properly controlled for nonascorbic acid reducing substances.

The titration of ascorbic acid using a xylene solution of 2:6 dichlorophenolindophenol has also been proposed (37). Interference due to SO_2 in fruit products may be eliminated by the use of hydrogen peroxide according to Levy (36).

A method for estimating ascorbic acid using whole blood or urine has recently been proposed by Roe and Kuether (38). Blood is deproteinized with trichloracetic acid, the ascorbic acid in the

filtrate is oxidized by norit to dehydroascorbic acid and a stable colored derivative formed with 2:4 dinitrophenylhydrazine in the presence of sulphuric acid. The color is read in a photoelectric colorimeter. The method is apparently specific and not affected by keto-acids. Glucose, fructose, pentoses and glucuronic acid do not interfere at levels ordinarily encountered in blood or urine.

The use of hydrogen sulphide in methods requiring the estimation of dehydroascorbic acid is not without its disadvantages. Recently electrolytic reduction (39) has been advocated, while another method proposes the use of a suspension of B. coli in glucose media (40) for the same purpose. The reduced ascorbic acid is then estimated by reduction of 2:6 dichlorophenolindophenol.

Plasma and blood methods. Following the earlier studies on hypovitaminosis C in which urinary excretion (41) of ascorbic acid was used as a criterion of depletion, methods measuring fasting blood plasma levels were developed (42, 43, 27).

Plasma was used to avoid difficulties arising from oxyhemoglobin of whole blood, which was later shown to enter into a coupled oxidation with ascorbic acid during deproteinization (44). By saturating blood with carbon monoxide before precipitation with metaphosphoric acid, Butler and Cushman (45) were able to estimate ascorbic acid in whole blood by oxidation-reduction dye methods. The use of lead acetate (46) with metaphosphoric acid deproteinization has recently been recommended for removal of sulphydral derivatives in whole blood analysis.

Because of the variation of plasma ascorbic acid levels with food intake, it has been recommended (45) that either whole blood or white-cell platelet ascorbic acid content be employed as a more reliable single index of body tissue saturation.

Kruse (48) has recently recommended the examination of the gingiva by means of the biomicroscope as a means of detecting early signs of vitamin C deficiency.

Requirements and utilization. Jolliffe has recently pointed out that "the diagnosis of nutritional failure cannot be limited to clinically manifest anatomical lesions. The preclinical states, as represented by tissue depletion, biochemical 'lesions' and altered physiology, hold greater import because they precede and are more common than the anatomical lesions (47)." Estimations of tissue saturation have been based upon measurements of the ascorbic acid level of the plasma, the whole blood, the white-cell platelet layer as well as tolerance tests based upon changes in plasma level and urinary excretion in response to oral or parenteral doses of ascorbic acid. Thysell (49) in a study of 233 subjects, showed blood levels of ascorbic acid of 1.0 to 2.0 mgm. per 100 ml. to follow the daily intake of more than 100 mgm. ascorbic acid, with other respective blood levels to intakes as follows: 0.4–0.8 mgm. per cent with 50–100 mgm. intake; 0.2–0.6 mgm. per cent with 30–50 mgm. intake; 0.0–0.4 mgm. per cent with 15–30 mgm. intake; and 0.0–0.2 mgm. per cent with less than 15 mgm intake. While it is generally agreed that the maintenance of fasting plasma ascorbic acid levels of 0.7 mgm. per cent or above is indicative of normal tissue saturation, low plasma values (0.0–0.4 mgm. per cent) unless found upon repeated examination, need not indicate a state of marked tissue depletion, and should not be taken as evidence of an impending scorbutic state. When such values are found, a determination of the ascorbic acid content of whole blood (45) or of the white-cell platelet layer may furnish evidence of the severity of tissue depletion. From studies on experimental human scurvy (50) low ascorbic acid values in cellular blood constituents would indicate a prolonged period of inadequate vitamin C intake.

As a result of placental transfer, the plasma ascorbic acid of the infant at birth is frequently higher than that of the maternal blood (51, 6, 52). Plasma levels at birth average above 0.60 mgm. per cent but decrease by nearly 50 per cent during the first 24 hours. On artificial diets without adequate vitamin C supplements, these values remain low, but with adequate intake either as a supplement or breast milk, they may attain values of 1 mgm. per cent at two weeks of age (53). A postpartum drop has also been observed in the mother (54).

Lund and Kimble (52) gave intravenous injections of ascorbic acid in doses of 100 to 500 mgm. to women before delivery and noted a rapid rise in maternal and cord blood; the foetal plasma level lagging somewhat, but reaching an equal concentration in 1½ to 2 hours. If the women were injected earlier than 2 hours before delivery, the maternal blood level decreased but the cord blood level remained high for at least 12 hours. On the basis of their observation, they suggest that ascorbic acid passes from maternal to foetal circulation by diffusion, at periods of high concentration in the former, and is blocked by the placental barrier from re-entering the maternal circulation. This theory seems plausable and if corroborated, would dispose of the question of foetal synthesis. On the other hand, living membranes have repeatedly been shown to exhibit selective permeability (55), and recent work shows ascorbic acid capable of functioning at cell surfaces (56).

As shown by Levine, Marples and Gordon (57) premature infants exhibit a spontaneous defect in their metabolism of tyrosine and phenylalanine which is manifest by the excretion of p-hydroxy-

phenyllactic and p-hydroxyphenylpyruvic acids into their urines if fed artificial diets in which the protein intake is 5 grams or more per kilogram of body weight per day. The relationship of vitamin C to the metabolism of aromatic amino acid has recently been reviewed by Sealock (58) and therefore need no further discussion here. It has also been shown that premature infants receiving human milk retain a larger part of a saturation dose of ascorbic acid in their tissues than do premature infants given cow's milk (59).

Breast fed infants of mothers on adequate vitamin C intake will receive 10 mgm. ascorbic acid daily until lactation is fully established when 20 mgm. or more is provided, increasing to 50 mgm. when weaned at 9 to 10 months of age (60). Artificially fed infants require a minimum daily intake of 10 mgm. ascorbic acid to prevent symptoms of scurvy (61). Plasma ascorbic acid levels are higher in breast fed infants than in those fed an artificial diet with a supplement of two ounces orange juice daily (62).

Ascorbic acid requirements for various age groups as summarized by Smith (65) are: Infants 8 to 50 mgm. daily; children 22 to 100 mgm.; adults 28 to 100 mgm. or more. Recent studies employing various criteria of saturation with subjects on controlled ascorbic acid intakes, indicate the following daily amounts to be required: Boys 10 to 14 years—45 to 75 mgm (64, 65); girls 6 to 12 years—62 to 72 mgm. (66); college students under 25 years—over 100 mgm.; older college women (25 to 50 years)—below 100 mgm (67). Observations on 800 youths at an N.Y.A. center indicated a diet containing 75 mgm. ascorbic acid to be inadequate (68).

Studies by Storvich and Hauck (69) indicated that daily supplements of 65 to 150 mgm. ascorbic acid in addition to 10 mgm. in the basal diet were required by six normal adults to maintain tissue saturation. In later studies (70), 10 of 12 subjects showed renal thresholds at plasma levels of 1.10 to 1.30 mgm. per cent. Of six subjects receiving 74 mgm. ascorbic acid daily for 12 to 14 days, three showed saturation and three slight depletion of tissue reserves. The authors also point out that subjects with high renal threshold levels maintain higher plasma ascorbic acid levels on lower intakes of ascorbic acid than do individuals with low renal thresholds. It is implied that this has a corresponding influence upon tissue saturation. The effect of a possible renal retention of ascorbic acid should not be overlooked when investigating tissue vitamin C saturation in clinical material (71, 72).

In reviewing the literature, one is impressed with the relative agreement as to daily ascorbic acid requirements considering the various criteria employed. In establishing the degree of tissue saturation, the test dose may be given orally as in most cases cited above, or by intravenous injection (73). In the oral tests, some gauge the dose according to the weight of the subject (65, 74) while others administer an arbitrary amount (usually 300 or 400 mgm. ascorbic acid) and base the criterion of tissue saturation upon the excretion of 50 per cent of the test dose into the urine in the following 24 hours. The adoption of a standardized technic for saturation tests under suitable sponsorship would help future attempts at establishing the proper levels of daily requirements. It is also apparent that the present recommendations of the Committee on Foods and Nutrition of the National Research Council for daily allowances of vitamin C are conservative, especially if the body is to maintain suitable reserves to successfully resist drains placed upon it by the onset of an infectious disease or other emergency.

Recent observations on the ascorbic acid requirements of certain lower animals are of interest. Hens under demand of heavy egg production when fed a vitamin C deficient diet may develop avitaminosis C resulting in leg weakness (75). Ascorbic acid when added to purified diets and liver supplements exerts a growth promoting effect in chicks (76). Ascorbic acid has been shown to be of therapeutic value in treating certain types of sterility in the cow (77). Later work indicates that vitamin C has a direct stimulating effect in maintaining fertility in the bull, stallion, jack and boar (78). Holstein calves may be raised from birth on skim milk supplemented with vitamins A, C, and D when given access to hay and grain (79).

The fate of orally ingested ascorbic acid. Loss of ascorbic acid after oral ingestion has been shown to occur in infants during diarrhea and following saline catharsis (80). With subsidence of the diarrhea, the fecal losses decreased with corresponding increase in urinary excretion. It has also been shown that on daily ingestion of ascorbic acid in amounts varying from 73 to 1054 mgm., the fecal excretion averaged 5 to 13.8 mgm. (81). Since a large part of the difference, especially at higher intake levels is excreted through the kidney, the balance must either undergo bacterial destruction in the gastrointestinal tract, or be utilized in some method as yet unknown by body tissues. Secretion during lactation (60) is definitely established, but secretion in sweat probably does not occur (82, 83, 84). Excess utilization in hyperpyrexia of non-infective origin is doubtful (85), nor does a high intake increase work output or exert any favorable influence during exposure to high environmental temperatures (86).

Decomposition of ascorbic acid by bacteria in the rumen of cattle has been established. Kendall and Chinn (87) demonstrated its utilization by organisms of the mucosus capsulatus and entero-

coccus groups, isolated by special methods from the gastrointestinal tract and feces of human beings. They also found that certain non-ascorbic acid fermenting bacteria (B. alcoligenes, Flexner type B. dysenteriae) exert a "protective action" upon the breakdown of ascorbic acid. The simultaneous rapid fermentation of carbohydrate also prevents the breakdown of ascorbic acid. Young and Rettger (88) later include as ascorbic acid fermenting organisms members of the following genera,—Escherichia, Aerobacter, Salmonella, Eberthella, Streptococcus, Encapsulatus and Vibrio. These observations, while indicating the susceptibility of ascorbic acid to destruction by intestinal bacteria when studied in vitro, need not be viewed with alarm except possibly in certain individuals whose intestinal flora may be overrun with ascorbic acid fermenting organisms. We may find in this work an answer to the occasional failure of oral therapy (except in massive doses) and the prompt response upon parenteral administration. The importance of the sparing action of carbohydrates for ascorbic acid when subjected to simultaneous bacterial action should not be overlooked. Studies of absorption of ascorbic acid by the small intestine in the human being, by the intubation technic, shows that 188 to 374 mgm. of ascorbic acid can be absorbed in one hour by a segment of small intestine 45 cm. long of subjects in either the saturated or depleted states (89).

Some observations on human subjects during prolonged ascorbic acid depletion.[1] Recent studies in prolonged vitamin C depletion in the human subject have sought to gain information by available methods, of changes in body chemistry and physiology as depletion progresses to the scorbutic state. Surgical studies have been concerned with the relationship of ascorbic acid to wound healing. The excellent study on "Experimental human scurvy" by Crandon, Lund and Dill (50) served largely as a guide for the study to be briefly outlined here.

Twelve young men, ages 20 to 30 years, were placed on a basal diet inadequate in vitamin C, and containing minimal quantities of the vitamin B complex. Five subjects remained on this diet, five received daily supplements of the B complex in amounts recommended by the Committee on Foods and Nutrition of the National Research Council, and two, serving as controls, received daily supplements of the B complex and 75 mgm. ascorbic acid, which was later raised to 150 mgm. Calories, protein, minerals and other vitamins were supplied in adequate amounts. The experiment lasted for seven months. Observations were made of the plasma and white-cell platelet ascorbic acid content, urinary ascorbic acid excretion, complete blood chemistry, hemoglobin, cell count and metabolic urinary constituents.

The diet was selected from a cafeteria, choosing those articles which were known to be free from ascorbic acid or which by over cooking, with and without soda, and holding on the steam table were shown by chemical analysis to be low or lacking in vitamin C. In this respect, our investigation differed from that of Crandon, Lund and Dill. A civilian might conceivably select a diet similar to ours. The ascorbic acid content while calculated at zero, might occasionally rise to 5 or 10 mgm. per day as shown by analysis.

The average time required for the plasma ascorbic acid to fall to zero was 70 days. Crandon attained the same point in 41 days. The white-cell platelet ascorbic acid dropped more rapidly in subjects deficient in both vitamin C and B complex, than those deficient in vitamin C alone. Zero levels in both groups were obtained during the latter part of the fifth month on the depletion diet. Crandon required 122 days to reach zero white-cell platelet content.

It was again found that capillary fragility measurements were an unreliable index of vitamin C deficiency (90). Crandon reports negative values by the same technic in his case. Serum phosphatase was unaffected by vitamin C depletion, remaining within a range of 1.89 to 3.91 Bodansky units for the depleted subjects, and 2.08 to 3.41 units for the normal controls. The observed decrease of phosphatase in the scorbutic infant (91) and scorbutic guinea pig (92) need not be considered contradictory to our results when it is remembered that phosphatase values in man are normally low after skeletal development has been attained. We were dealing with young adults 20 to 30 years of age.

Studies on work output were made by Dr. Eliot E. Foltz through the courtesy of the Department of Physiology, using an electrodynamic brake bicycle ergometer. Subjects in both depletion groups showed a measurable decrease in work output, that of the controls remaining constant. Evidence that vitamin C plays a minor part, if any, in the performance of work has been presented by Keys (93) in a recent review. Our subjects complained of severe fatigue during the last two months of depletion.

Neurological and psychological tests were made by Dr. G. K. Yacorzynski of the Department of

[1] The work described in this section was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Northwestern University. Unpublished data by C. J. Farmer, A. F. Abt, D. Y. Burrill, W. W. Carroll, M. Dentler, E. E. Foltz, D. O. Manshardt, J. A. Wolfer and G. K. Yacorzynski.

Nervous and Mental Diseases. His observations may be summarized as follows: The choice reaction time increased after the third to fifth months on the deficiency diet. Individuals making the greatest number of errors in choice reactions or whose reaction time shows great variation, appear to show the greatest debilitating effects of vitamin C depletion. The latter effect is associated with loss of interest or motivation. Characteristics such as aggressiveness, submissiveness, etc., become exaggerated during depletion. Under the conditions of our investigation, no measurable effect attributable to vitamin C depletion could be observed in certain tests including threshold of perception, coordination of motion on a pursuit meter and critical fusion frequency of visual flicker.

A study of oral changes attributable to acute ascorbic acid depletion was made by Dr. D. Y. Burrill of the Department of Oral Pathology, of the Dental School. The teeth of all subjects were scaled, the necessary fillings made and a program of oral hygiene instituted at the beginning of the study. Periodic checks and a final examination revealed no sponginess of gums or bleeding tendency. Examination of gums with the biomicroscope and slit lamp revealed no insacculation or capillary abnormalities. No changes in bone structure were revealed upon X-ray examination. The lack of oral pathology in our subjects, and the observation of but a single small gingival hemorrhage by Crandon, Lund and Dill (50) suggest that oral conditions frequently ascribed to an acute inadequate intake of vitamin C may in reality be due to a pre-existing caries or to improper oral hygiene. It cannot be questioned that severe oral lesions follow protracted depletion of vitamin C as evidenced by lesions around erupted teeth in the scorbutic infant (119), the interruption of the lamina dura, indicating a beginning atrophy of the alveolar bone as observed in x-rays by Crandon, and the familiar loosening of the teeth in the scorbutic guinea pig.

Studies of wound healing were made by Drs. J. A. Wolfer and W. W. Carroll of the Department of Surgery, and histological examinations by Dr. D. O. Manshardt, Pathologist of Passavant Memorial Hospital, on all depleted and control subjects during the seventh month of depletion. An incision 6 centimeters long was made through the skin and fascia of the left thigh. After properly suturing, biopsy sections were taken of the skin and fascia, from the 5th to 14th day of healing. The biopsy sections were removed in such a way that both cruciate and lineal closures of the skin were affected. The biopsy specimens were used for histological examination and also for measurement of the strength of tissue at the suture line [rupture factor = $\frac{\textit{grams to rupture at suture line}}{\text{area at suture line, (sq. mm.)}}$]. The rupture factor paralleled depletion as indicated by ascorbic acid saturation tests. Histological examination of the skin and fascia in the depleted subjects showed a marked deficiency of reticulum and collagen. (See Photomicrographs.) Similar results were obtained by Crandon.

A marked susceptibility to wound infection, especially in the severer type of wound resulting from cruciate closure accompanied vitamin C depletion. (See Fig. 1, severely depleted subjects.) The dependence on adequate reserves of vitamin C in tissues for wound healing, and for other functions, has been shown by several investigators for both the human subject and experimental animals (50, 94, 95, 96, 97, 98, 99, 100). A distinction is made by Chambers and Cameron (101) between

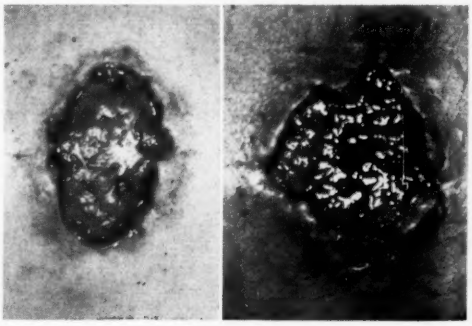

Fig. 1. Photographs of wounds in severe vitamin *C* depletion. Diet vitamin *C* deficient—*B* complex minimum. Mahoney (left) on eighth day and Mallette (right) on eleventh day after biopsy with cruciate closure.

the requirement of ascorbic acid for formation and maintenance of interstitial matrices (dentine, bone, collagen in connective tissue) and the non-essentialness of ascorbic acid for production and effectiveness of intercellular cement.

Periodic physical examinations were conducted by Commander A. F. Abt, U.S.N.R. No evidences of clinical scurvy were observed except hyperkeratotic papules surrounding the hair follicles on the lower extremities. The latter were observed by Crandon at an earlier date on his more rigourous diet. Although spontaneous capillary hemorrhages never occurred in our subjects, several areas around the wounds showed petechiae resulting from the slight trauma attending surgical manipulation. No such areas were observed on the normal control subjects.

Following the surgical studies, all subjects, except the two who were hospitalized because of severe wound infection, received by mouth a test

dose of 15 mgm. of ascorbic acid per kilogram of body weight. Their degree of tissue saturation was judged from the behavior of the plasma ascorbic acid curve, its magnitude of rise, and the hourly excretion of ascorbic acid into the urine, during the subsequent five hour period. Typical curves are given in figures 2 and 3. These, together with the results of the surgical studies, indicate the saturation test as described here to be a convenient and reliable index of tissue depletion. These studies further indicated that daily intakes of 100 mgm. ascorbic acid for one month provide adequate tissue saturation for a maximum rate of tissue repair in healthy young adults. Even lesser amounts are indicated by the behavior of one subject (Robley), emphasizing the rôle of individual variations, or possibly a less rigid adherence to a prescribed diet. These studies will be reported elsewhere in full at a later date.

acid may be related to the animal's detoxification processes.

Sulzberger and Oser (105) in 1935 showed that guinea pigs on diets inadequate in vitamin C, are more easily sensitized to neoarsphenamine by intracutaneous injection than controls on adequate diets.

In 1937, Dainow (106) reported a favorable influence of ascorbic acid upon arsphenamine tolerance in the human being. Many of his subjects were judged to be on inadequate vitamin C intake as evidenced by the lack of urinary excretion of this substance. Plasma ascorbic acid levels (107) are depressed in some cases and not in others (108) by administration of neoarsphenamine. It has been shown by Bundesen, Aron, Greenebaum, Farmer and Abt (109) that the dermatitis developed in human subjects when patch tested with various arsenicals may be prevented in a large proportion

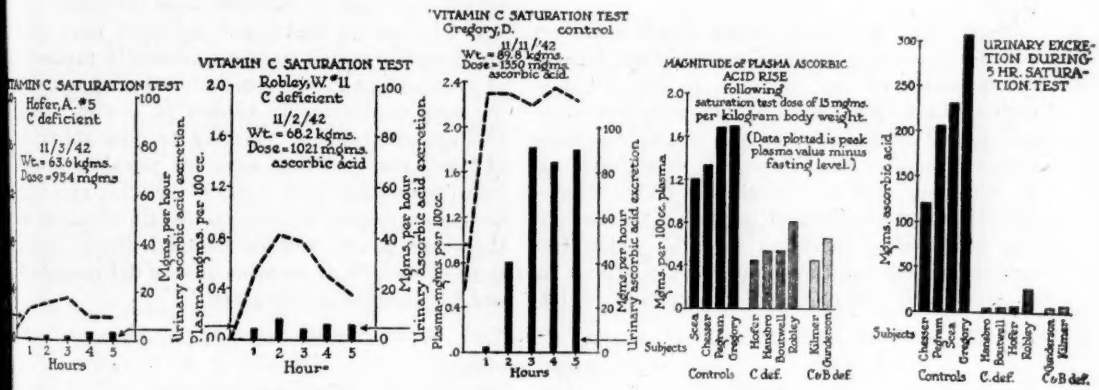

Fig. 2a Fig. 2b Fig. 2c Fig. 3a Fig. 3b

Figs. 2 and 3. Vitamin saturation tests

Miscellaneous conditions apparently influenced by ascorbic acid. In conclusion, a word should be said regarding the rôle of ascorbic acid in certain drug intoxications, the anemias and one or two other conditions.

It has recently been reported that scorbutic guinea pigs show extensive hepatic damage when injected with hydrazine (102) while control animals receiving 30 mgm. ascorbic acid daily were completely protected. Evidence that pathologic changes may occur in the parenchymal cells of the liver, and in the proximal convoluted tubules, in the guinea pig as a result of scurvy has recently been reported (103). Longenecker, Fricke and King (104) have shown an increased excretion of ascorbic acid into the urine of albino rats after administration of certain hypnotics and antipyretics. While there was no evidence of conjugation of ascorbic acid with these drugs, it is suggested that the endogenous production of ascorbic

of cases, by admixture with ascorbic acid. Neoarsphenamine and mapharsen solutions exposed to air are quickly oxidized to a brownish-black color. The addition of ascorbic acid markedly retards this reaction. Recently McChesney, Barlow and Klinck (110) have shown that the toxicity of neoarsphenamine for albino rats is materially reduced by ascorbic, isoascorbic, d-glucoascorbic and p-aminobenzoic acids. The most favorable effect was obtained when the arsenical and protective agent were injected simultaneously in the same solution. The function of ascorbic acid appears to be primarily that of preventing oxidation, chiefly after injection. Much clinical data has accumulated in evidence of the amelioration of symptoms of toxicity when arsphenamines are administered with ascorbic acid (106, 111, 112, 113).

Studies on the relationship of vitamin C to anemia are numerous. Anemia usually ac-

companies the production of scurvy in the growing guinea pig (114). Administration of some source of vitamin C (115) improves the blood picture unless the animal has lost more than 25 per cent of its body weight or one-third of its hemoglobin (116). A specific erythropoietic action has been attributed to vitamin C (117), but other investigators have failed to associate anemia, at least in the adult, solely with a vitamin C deficiency (50) but concomitantly with infection, general malnutrition or iron deficiency (118, 119, 120). It has been shown that patients with pernicious anemia on adequate vitamin C intakes have a significantly lowered plasma ascorbic acid level while patients on similar diets with an iron deficiency anemia show normal levels (121). The administration of ascorbic acid concomitantly with liver therapy has been successful in causing remission of symptoms in a series of pernicious anemia patients following unsatisfactory response to liver therapy alone (122).

Many other important observations could be added, for example the development of oral lesions accompanied by an increase in the fusospirochetal flora by Macacus mulatta monkeys when maintained on diets deficient in certain members of the B complex but adequate in vitamins A, C, D, nicotinic acid and riboflavin (123). Glucoascorbic acid when fed as 10 per cent of the dietary has produced a condition in mice which the authors consider as the counterpart of scurvy in other animals (124). A final observation, which may be of importance in the field of aviation reports that exposure of human subjects at a simulated altitude of 18,000 feet for one hour every second or third day, disturbs the metabolism of vitamin C (125). The immediate effect was a decreased urinary excretion of ascorbic acid followed later by a compensatory excretion of large amounts of this substance. Guinea pigs injected with 100 mgm. ascorbic acid when exposed to a simulated altitude of 18,000 feet for 12 hours showed a higher plasma and muscle ascorbic acid content than control injected pigs remaining at normal atmospheric pressures.

Conclusion. An attempt has been made to bring together information as to food sources of vitamin C and the influence of certain methods of handling and cooking upon the ascorbic acid content. A brief review of methods for analysis of food, and body fluids is given. Requirements ascertained for various age groups are indicated. Studies on depletion of human subjects have furnished evidence indicating that tissue depletion requires a considerable period to affect adversely processes of surgical repair. It is also shown that an individual may inadvertently subsist on a diet which through processes of handling or poor selection of foods may without apparent physical symptoms, reduce his body stores of ascorbic acid to a dangerous degree, leaving no margin of safety in the event of any unusual demand. Brief discussions of the rôle of ascorbic acid in detoxification and the anemias is also given.

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AMERICAN PHYSIOLOGICAL SOCIETY

Symposium on Physiological Aspects of Convalescence and Rehabilitation

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INTRODUCTION TO THE SYMPOSIUM ON CONVALESCENCE AND REHABILITATION

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The practical needs for knowledge of the physiological factors in convalescence and rehabilitation are well stated in this symposium by Doctor Tillett and by Colonel Rusk. Specific points of outstanding clinical and scientific uncertainty are exemplified on every page of the succeeding papers. It was recognized at the outset that this symposium would consist primarily of questions rather than answers but it seemed desirable to bring together such information and opinions as could be offered by a panel of experts representing a wide range of specialties.

The war has forced the emergence of a larger physiology than has been recently characteristic of the academic view of the subject. While it would be regrettable to curtail the more purely Aristotelian approach it must be admitted that the physiology of man as a whole, including psychological aspects and applied physiology generally, has too often received rather cavalier treatment. In extenuation of the physiologist it should be noted, however, that suitable facilities and personnel needed for detailed and controlled studies on man are rarely available in either universities or hospitals. Such work is expensive and demands intensive collaboration between specialists representing several sectors of the broad science of physiology. Animal experiments yield a rich reward of accurate data but they are inherently limited to the analysis of parts of the broader problems. It must be realized that knowledge of the whole is not readily synthesized from the minute inspection of some of its parts. Furthermore, species differences prevent detailed predictions for man and other animals.

The contributors to the present symposium were repeatedly urged to abandon the narrow conservatism of factual citation in favor of the expression of opinions and ideas not necessarily buttressed by all the paraphernalia of pedantic scholarship. In the essential absence of directly pertinent information a mere recital of claims or of findings in situations only remotely analogous to the real problems would be futile. Some boldness is necessary to make a symposium of ideas.

Perhaps the chief function of this series of discussions is to clear the way for the real fact finding to come. It is hoped that much new research will be stimulated by the present exposition of problems and expression of ideas. Powerful motivation may result from disagreement with some of the present opinions. A deliberate attempt has been made to provide targets to shoot at; of necessity this means that many of us have ventured on to more remote limbs than is our customary wont.

An effort has been made to force consideration of some of the psychological aspects of convalescence and rehabilitation. This is especially apparent in the contributions by Taylor and Brozek, Dunbar, and Goldstein. As a matter of fact, previous efforts in rehabilitation have been largely in the psychological field but distinction should be made here between general bodily re-building and vocational rehabilitation. The latter includes some therapeutic applications but is often confined to special job placement.

A notable omission from the present group of contributors is primary representation from physical education. It is unfortunate that work in physical education is too remote in method and principle from our hospitals and laboratories in the fundamental sciences. We may hope for some improvement from the rather tentative efforts in a few universities, such as Harvard, Indiana, Wisconsin and Minnesota.

In science generally progress is slow in proportion to the complexity of the subject. Surely no questions are more complex than those of convalescence and rehabilitation, but it may be hoped that efforts more commensurate with the scientific and social importance of these problems will vastly increase our knowledge. We need not judge the field to be barren because in the uncultivated state its products have been few and of dubious merit.

THE NEEDS FOR PHYSIOLOGICAL KNOWLEDGE: CIVILIAN MEDICINE

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If an attending physician when making rounds on the wards of a general hospital asks himself at each patient's bedside the question why is this patient kept at complete bed rest, the answers are interesting to consider and are liable to be, in a surprising number of instances, vague in their content. The degree to which bed rest with its accompanying physical inactivity is entrenched as a routine part of orthodox medical care, particularly hospital care, is illustrated in a very obvious and simple fashion by noting that the size of a hospital is traditionally referred to in terms of "bed capacity." The principle reason for the limited attention which the general aspects of the management of sickness have received is accounted for by the concentrated interest which medical studies have given to the pressing problems of individual diseases with respect to specific etiology, essential nature, and specific therapy.

In the present rising scientific interest in the field of convalescence and rehabilitation, the range of medical studies is being broadened beyond disease entities by directing special attention to that period of sickness which is primarily concerned with recuperative processes leading to ultimate recovery and also with the maintenance of the normal functioning of as much of the body as possible in spite of the persistence of permanent disability or of the presence of some, as yet, irreversible pathological change. In accomplishing this purpose the greatest progress may be expected to emerge from applying the same principles of exactness in observation and research methods to the complicated elements involved in the convalescent state that have been so successfully utilized in studying specific maladies that are primarily responsible for morbidity.

Although the subject is a broad one, the physiological aspects of the problem are particularly well illustrated by reviewing the bases for the essentially routine medical procedure which utilizes bed rest for indeterminate periods of time as the most conspicuous adjunct to any other form of medical treatment.

Without belittling the charm and comfort of repose or minimizing its restorative value for acute fatigue it is pertinent to attempt to assay the effects of protracted physical inertia on the patient's course. As an aid in identifying the special problems that invite technical study in this field the query posed at the beginning of this article may be subjected to detailed analysis based on present knowledge and current medical practice.

In discussing the topic it is unnecessary to include a consideration of the presenting necessities which require that a patient be put to bed immediately on admission to the hospital. Factors involved in the patients immediate needs and comforts in the procedures of clinical and laboratory examination, and in estimating the severity of the disease under basal conditions are circumstances which are self evident.

However, after the diagnosis is made and the plan of treatment directed toward the specific malady is instituted, the reasons for the subsequent enforced periods of passive relaxation invite detailed consideration.

Expressed in broad terms, the chief purpose of bed rest during sickness is to reduce to a minimum the activity of the parts of the body or the physiological systems that are involved in the disease processes. This therapeutic conviction is based on the medical belief that optimum healing of areas of disease require inactivity of the affected part and that readjustments of pathological physiology are dependent upon minimal functioning of the system involved. Patients being as a rule intact organisms, the means by which the diseased organs or systems are given the advantages of maximum bed rest result in the patient as a whole being involved in protracted periods of inactivity. The resulting total inactivity, therefore, creates through disuse, damage to functions that are otherwise normal while at the same time permitting damaged tissues to undergo repair. The crux of the problem of convalescent care lies within this paradoxical situation.

As the course of hospitalization proceeds the decision as to when the patient may bestir himself is based on clinical evidence of considerable improvement or complete clearing of the organic disease plus—and often the most influential reason—the patient's wishes in the matter. In the absence of either one or both of these indications, or when changes in the pathological processes occur slowly or not at all, the continuation of the period of physical inactivity is usually assumed by both physician and patient to be the accepted course of convalescent care.

Against the background of medical management which has been briefly outlined in the preceding paragraphs, it is interesting to consider how much

of it is based on objective data obtained by valid methods of observation.

On the basis of clinical experience supported in part by pathological and physiological observations it is possible to list the abnormalities for which complete inactivity is most clearly indicated. They are:

Reducing the demand exacted by physical exertion on a cardio-vascular and respiratory system rendered incompetent by disease and further embarrassed by muscular effort;

eliminating pain and alleviating other distressing symptomatology and anxiety referable to physical movement;

promoting the sustained approximation of healing surfaces by immobilization;

fixing as much as possible areas of acute inflammation;

arresting hemorrhage or preventing its recurrence.

At the height of any illness characterized by the presence of any one of the serious abnormal manifestations listed above, the indications for complete rest appear authentic. However, after the acute phase has subsided, the extent to which the period of inactivity should be continued depends at present on individual subjective medical opinions, which are, for the most part, empirical.

Within this field which comprises the convalescent state there are two needs for guidance that clinical medicine does not possess. The first deals with methods of objective measurement by which the extent of damage to any system involved in the disease process may be measured with precision and by which the rate of return of its function to normal may be followed.

The second requirement concerns alterations occurring in other systems of the body caused, on the one hand, by the sympathetic or indirect effects of the primary disease and, on the other hand, by the depressed functions referable to sustained periods of inactivity.

The physically weakened and organically inefficient state in which the body is left after the stormy events of active disease have subsided is made up of numerous elements of an anatomical, physiological, biochemical, and psychological nature that interact in a complicated fashion.

An understanding of the origins and relative importance of these factors await the results of investigations that involve essentially every field of research, particularly those dealing with function.

Although the tenor of the remarks so far elaborated in this report have implied that when no positive indications for complete bed rest are apparent in the patient's clinical state, its use is not only not beneficial but is even harmful, it may also be equally emphasized that the institution of physical exertion without utilizing accurate methods of estimating its effect is subject to the same criticism. In this connection it is important to mention that one of the fallacies in physiological measurements, particularly when disease is present, rests upon the assumption that results obtained under *basal* conditions represent the state of an organ and its capacity to function under *normal* conditions. Since the basal conditions for most tests require that an individual remain in the supine position with minimal physical, mental and metabolic activity for specified periods of time and since the normal conditions of living are accompanied by movement, exertion, cerebration and active metabolism that are operative during periods of erect posture, it is obvious that the findings under each set of conditions may not be interchangeable. Measurements of the capacity and range of function are more serviceable for properly controlling convalescent care than are repeated estimates of basal function.

By way of summary, one of the important contributions that may be expected to emerge from studies directed along the lines indicated in this article is that the management of the convalescent period of sickness will cease to be a non-specific empirical procedure but will take its place among the specific forms of therapy directed purposefully toward well defined organic and functional abnormalities.

Under these circumstances it may be predicted with confidence that the clinical sciences will exhibit the same active interest in the processes and the treatment of the recuperative phase of disease that they have formerly given to the primary disease entities since with this increased sphere of knowledge, vague elements included in such expressions as debilitation, weakness, and invalidism become identifiable disorders the control of which may be approached with technical accuracy.

It may also be envisioned for the future that in civilian hospital management, and also in hospital construction, the center of emphasis can be transferred from "bed capacity" to include broader interests which individualize the restorative requirements needed by patients according to intelligent tangible indications that extend beyond the bedposts.

THE NEEDS FOR PHYSIOLOGICAL KNOWLEDGE: THE ARMED SERVICES

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In the past three decades the science of medicine has made impressive advances. Surgery, pathology, biochemistry, bacteriology, and physiology each have added their contribution to the great pyramid of scientific medical knowledge. The practicing physician has been overwhelmed by an avalanche of technical knowledge far too great for any one man to assimilate fully and utilize in an orderly fashion. In attempting to evaluate, crystallize, and put into terms of effective treatment this great mass of scientific data for each individual patient, the physician has been compelled to focus his attention primarily on the therapeutic application of medical science. The *disease* has been treated, but more than occasionally, the *patient* has been neglected. When the medical or surgical crisis has passed and the curtain has been drawn on the drama of the necessity for immediate decision and action, the busy physician has been prone to allow his patients to drift aimlessly through the days of convalescence without chart or rudder. Needless days have been lost from productive activity, relapse has been common, and boredom constant in the grey days of convalescence.

The need for a planned, supervised, and progressive program of convalescence is a military necessity in time of war. In the Army, a soldier is either sick in the hospital or on full military duty. Bed rest and idleness are not conducive to physical fitness. The human body does not remain static. Bed rest often is necessary, but bed rest brings about "deconditioning," and this must be counteracted by specific "reconditioning." Reconditioning must be both physical and mental, and to be effective must follow the cardinal principles known to all practitioners of medicine. As in any type of therapy, it must start early and be a continuous, progressive, and uninterrupted process to the point of successful completion.

Individuals engaged in flying are subjected to unique physiological stresses rarely encountered in any other occupation. It becomes necessary therefore for the physician practicing aviation medicine to acquaint himself with these stresses in order that they may be prevented insofar as possible, and if they occur, be treated on a sound physiological basis. The flight surgeon is engaged in a never-ending effort to attempt to maintain a normal physiology in flying personnel through indoctrination in the physiological effects of flying and to combat the effects of abnormal physiological exposure by the use of secondary devices. A concrete example of this work is the AAF Altitude Training Program—one of the largest physiological teaching programs ever devised for a specific occupation.

The physician in aviation medicine, then, is faced not only with the necessity of acquiring a sound physiological basis for the practice of the usual type of medicine but also of acquiring a sound physiological knowledge on which to base the treatment of injuries encountered as a result of the abnormal physiology which may occur in flying.

Physiology has already made invaluable contributions in the field of aviation medicine. Oxygen deficiency, aeroembolism, motion sickness, decelleration, and frostbite are a few of the major problems that have been given to the physiologist for solution. Tremendous strides have been made in research in these fields. The opportunities for further research in these and kindred physiological subjects are myriad.

In order that convalescence of the sick and wounded may be put on a scientific basis it is an absolute necessity that the basic physiological facts be known. What does bed rest really do to the human organism? What is the significance of the biochemical changes as a result of bed rest in both the normal and the sick? What tests can be used to guide the physician in gauging the degree of convalescence attained and in prescribing activity, diet, and proper physiotherapy procedures? What is the optimum period of bed rest in acute infections? What effect has the maintenance of top physical fitness on the fixed parts in orthopedic injuries? When should brain injuries become ambulatory and by what criterion? To what extent is complete bed rest a physiological procedure in tuberculosis and rheumatic fever? These are only a few of the questions that pose themselves to the medical officer responsible for the convalescent training and rehabilitation of the disabled soldier.

The AAF has operated successfully a program of convalescent training and rehabilitation since December 1942, and numerous basic physiological problems have presented themselves in this field.

The need for sound physiological knowledge in convalescence and rehabilitation is basic. Military medicine looks to the physiologist for help in this ever-broadening field of medicine.

ENERGY METABOLISM AND CALORIC REQUIREMENTS

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The individual recovering from disease, injury, or chronic under-feeding is in need primarily of realimentation to restore him to health and normal activity. His food supply has been limited by the disinclination to take food or by the inability to obtain it. He is generally existing on a low metabolic level, but if the primary damage to his system inflicted by disease or trauma has been halted, his realimentation can be promoted according to the established principles of the science of nutrition. If the malnutrition induced by disease, injury or underfeeding relates to certain specific essential dietary factors, obviously realimentation must be directed primarily to the correction of these deficiencies by proper dietetic measures. But whether or not specific deficiencies are in evidence, the secondary, if not the primary, goal of realimentation is to secure not only an adequate consumption of food energy, but an excessive consumption to build up the body to its normal size and efficiency.

The energy requirements of the body and the disposal of food energy are different phases of the metabolism of energy. Energy transformations are intimately involved in all of the biochemical reactions occurring within the tissues and the cells; whether the transformation of matter or of energy is the more important depends in general upon whether the reaction is synthetic or analytic in character. If synthetic (anabolic), the physiological purpose of the reaction is to produce material substances for the construction of new tissue or for the maintenance or repair of old tissue. The energy transformation is of only incidental importance, though for many synthetic reactions, energy is absorbed and must be supplied by simultaneous analytic, or catabolic, reactions. Thus, the conversion of glucose to fat (6) seems to involve the absorption of an amount of energy equivalent to what would be produced by the oxidation of about one-fourth of the amount of glucose converted.

The predominant purpose of analytic (catabolic) reactions is to liberate the potential energy of food nutrients for the performance of physiological work, involved in the pulsations of the heart, the movements of the respiratory muscles, the performance of mechanical work by the voluntary muscles, and of chemical work by the glands of the body. During the performance of physiological work, the energy liberated by the catabolic reactions is dissipated from the body as sensible heat, except to the extent that work is done upon the environment, in which case energy is stored in the environment, as in winding a clock or climbing a staircase, or its dissipation as heat occurs outside of the body, as in pedalling a bicycle. Therefore, the measurement of the heat emitted from the body under conditions such that work is not done upon the surroundings, is a measure of the energy produced in metabolism when sensible heat is not stored within the body to produce a rise in body temperature.

The physiological work that a man performs and the energy he produces is in a very real sense a composite measure of the life activities, although not a fair measure of the cultural or social values of such activities, since mental work, in contrast to muscular work, involves an insignificant expenditure of energy (2).

The ingestion of food imposes a certain amount of physiological work upon the body in effecting its digestion, its progression along the alimentary canal, the excretion of undigested residues, the absorption of the end-products of digestion, the transportation of these products to the tissues, and the excretion of the end-products of their metabolism by the lungs and the kidneys. Also, the influx of the end-products of digestion into the tissues stimulates their rate of metabolism. In consequence of all of these factors, but particularly of the latter, the energy production of the body is increased as a result of the taking of food. This increase in energy production, is the so-called specific dynamic action of food.

The total energy produced in the body consists, for all practical purposes, of the following main factors:

(a) The basal metabolism including those energy transformations involved in the mere maintenance of life, the "cost of living" in terms of energy. For persons in normal health and nutritional status, the basal metabolism proceeds at a rate proportional to the surface area of the body and to age, and may be estimated with an accuracy of 10 or 15 per cent from any of a number of prediction equations. In undernutrition and convalescence the basal metabolism may be depressed by 20 to 30 per cent. In psychoneurotic individuals, on the other hand, emotional reactions may elevate the basal metabolic rate by as much as 40 per cent (29).

(b) The incidental muscular activities of the body involved in normal living, and in sedentary work. They include those movements essential to the care of the body and its nourishment, to enter-

tainment and social intercourse, and also those movements incidental to effective mental work. For lack of a better term they may be called the "energy increment of effective living," and, together with the basal metabolism, they constitute a minimum cost of effective living, again in terms of energy. The energy increment of living is commonly assessed at 50 or 60 per cent of the basal metabolism, though it obviously may vary greatly depending upon temperament and habits of living, and particularly upon age. In the active child, the energy increment of living may amount to 75 per cent of the basal metabolism (17), while in the aged it may shrink to 20 or 25 per cent. In convalescence it may drop to 10 per cent during confinement in bed.

(c) The energy expended in effective muscular work in manual labor. This quota of energy is related to the amount of work done. When the work can be measured, the energy expenditure may be estimated at 4 or 5 times the heat equivalent of the work done, since the human organism works generally with an efficiency of 20 to 25 per cent. In convalescence, this degree of muscular efficiency may still hold with little deviation. If the work is so complicated, as the work of typewriting, that it cannot be readily measured, the required expenditures are determined experimentally and expressed in calories per hour. Such determinations have been carried out for many kinds of domestic, industrial and agricultural labor. A compilation of many of these measurements of energy expenditures in effective manual labor has been published by Orr and Leitch (23). In hard manual labor, the rate of energy expenditure may amount to 8 or 10 times that of the basal metabolism.

(d) The energy expended in athletic sports. The work performed in some of these activities may be estimated with satisfactory accuracy, from the body weight and the height it is raised, or from the weight of a heavy object and the distance it is cast. But competitive sports and games are not of this character, and the energy expended in their performance, rather than the work done, must be directly determined. Some such determinations are given in the article of Orr and Leitch (see also 28). Others are scattered through the literature. An athlete may attain a rate of energy expenditure of 20 times the basal rate, or, in intense efforts lasting only a few seconds, a rate of 70 to 100 times the basal rate.

(e) The energy expended in the specific dynamic effect of food. This quantity of energy is related to the amount and character of the food consumed. Commonly used estimates for man are either 6 or 10 per cent of the fuel value of the diet. High-protein meals exert a greater specific dynamic effect than low-protein meals (3), and under conditions of rapid deposition of fat, as may occur in realimentation from disease and underfeeding, excessive heating effects of food may be expected (6, 24).

For an adult organism, exclusive of the pregnant or lactating woman, the sum of the energy expenditures from (a) to (e) inclusive, represents the energy requirement of the body. They result from the catabolic reactions of metabolism, since in adulthood catabolism greatly predominates over anabolism. Even in childhood, the anabolic reactions are quantitatively insignificant because of the slow growth rate of the child (7). The daily formation of new tissue in child growth ranges from 50 to 52 grams in the month-old infant to 4 or 5 grams in the pre-school child, rising again to 18 to 20 grams in the adolescent (18). Assuming that this daily increment in body weight possesses an energy value of 1 cal. per gram in the infant to 1.5 cals. per gram in the adolescent, the energy content of the new tissue formed daily would, at its maximum, not exceed 52 cals., and for most of the growth priod would range from 6 to 30 cals. In convalescence, the daily energy stored in rehabilitation may conceivably exceed these figures greatly, though no information on this point is available.

In the pregnant woman, the formation of fetal tissue is equivalent at term to a daily storage of only 20 to 25 cals., and this represents the maximum rate of intra-uterine growth. In lactation, with the milk flow ranging from 500 to 1000 cc. daily, the dietary energy thus stored would equal the considerable quotas of 320 to 640 cals.

The sum of this stored energy and of the energy expenditures above listed will give the total energy required by the child, the convalescent, the pregnant woman, or the lactating mother. Thus, the estimation of energy requirements is a mathematical procedure, the accuracy of which will depend upon the extent to which an individual's physiological activities can be analyzed, and, when thus analyzed, evaluated in terms of energy. A very practical phase of the science of nutrition is the evaluation of human activities in terms of energy expenditures. There is a great need of further studies of these energy factors in the convalescent (8, 24).

The satisfaction of the body's requirement of energy is, in practical nutrition, left entirely to the appetite. And dietary studies have shown that the appetite to a remarkable degree adjusts the intake of food energy to the requirement in the healthy individual in the great majority of cases. In contrast, the human appetite cannot be relied upon to adjust the intake of the essential nutrients to the requirements for those nutrients. In a remarkable comprehensive study of the nutrition of a population in Maine, Dove (9) has detected

only a very moderate correlation between the nutritive value of foods and their acceptability to consumers, represented by a correlation coefficient of only $+0.28 \pm 0.04$.

From these facts, one might infer that the need for energy is paramount in human nutrition. This seems to be recognized in the rationing of the army. Wodicka (27), after reviewing briefly recent advances in the science of nutrition, makes the following statement:

"Paradoxically enough, in military subsistence, these recent epoch-making advances are distinctly secondary in importance to a fundamental nutritional principle which must have been at least suspected by the cave man—namely, that a man must have enough to eat. In Army rations, the calorie takes precedence over the microgram.

"This order of priority has not been established by fiat or even by a conference of learned men. Repeated tests, both in physiology laboratories and in the field, have shown that a deficiency in calories results in impaired performance and poor morale more quickly and more markedly than a deficiency of any specific nutrient."

Not only is the need for food energy paramount in human nutrition, but to a large extent the energy consumed determines the requirements of specific nutrients. This is recognized in the recommended dietary allowances of the Food and Nutrition Board of the National Research Council, in that the allowances for thiamin, riboflavin and niacin are proportional to the caloric intake. Quoting the report giving these allowances (11): "This relationship has been established for thiamin, and it has been assumed to hold also for riboflavin and nicotinic acid, since, like thiamin, they are part of the enzymic system involved in the metabolism of carbohydrate."

The interrelationships of the nutrients in nutrition are such that one might expect that the need for any one nutrient is dependent upon the presence of others, and particularly upon the intake of organic nutrients that replenish the "metabolic mixture" from which the cells derive the energy for all types of physiological work. This might be presumed to be true at least for those nutrients, including minerals and vitamins, whose functions are concerned in promoting and regulating the rate of liberation of energy from the metabolic mixture. Presumably, it would not apply to those nutrients, such as protein, calcium, phosphorus and possibly vitamin A, the main function of which is to contribute to the structure of the tissues or organs of the body, or to the maintenance of the integrity of these structures against inevitable erosion by catabolic processes.

The conception of the balanced diet is based upon this assumption. The more of a balanced diet that is consumed by an animal up to the point of the repletion of its energy requirements the better nourished will it be. Conversely, the more of an unbalanced diet that is consumed, by which is meant a diet inadequate in one or more essential nutrients, the poorer nourished the animal becomes. Amantea (1) and Westenbrink (26) have shown that the time of occurrence of the characteristic deficiency symptoms of polyneuritis in experimental animals is directly dependent upon the amount of deficient food consumed, such that the greater the intake of food the quicker the disease develops. Famiani (10) has observed the same relationship between the onset of scurvy and the ingestion of a scorbutogenic diet. Similarly, the greater the consumption of a rachitogenic diet the slower is the rate of calcification of the bones (25), and the more milk rats consume the quicker will nutritional anemia develop (19, 22). Such evidence indicates that the need for thiamin, ascorbic acid, vitamin D, iron and copper, at least, is proportional to the amount of food energy to be metabolized, since, when the proportions are inadequate, the respective deficiencies appear in the tissues the sooner, the greater the rate of oxidation of the metabolic mixture. The complete withdrawal of food is a cure for deficiency symptoms or alleviates them, while factors that increase energy metabolism, such as fever, hyperthyroidism, pregnancy, lactation, and excessive muscular work, will precipitate deficiency crises that otherwise would remain latent (14).

The relationship between the content of essential nutrients in a diet and its content of food energy to be metabolized is a reciprocal one, since an inadequacy of a given nutrient seems to impair the utilization of the food energy by increasing the specific dynamic effect of the diet. Such an inverse effect has been demonstrated for protein (12, 20), riboflavin (5), and phosphorus (21), when the stores of these nutrients in the body are depleted to the extent that they do not effectively supplement the inadequate diets in these respects.

It appears, therefore, that the body's primary need for nutriment is for food energy, and that its need for most of the specific essential nutrients is in proportion to the amount of food energy consumed. This is an important principle in practical nutrition, especially in the nourishment of individuals with a prior history of malnutrition under conditions of limited food supply.

The victims of disease and chronic underfeeding have been living partly on a restricted diet and to some extent on their own bodily supply of fat and protein. Their basal metabolic level may be lowered 20 to 25 per cent if underfeeding relates to energy only, or it may be raised somewhat if specific nutrient deficiencies are prominent, judging from animal experimentations (15, 16). The efficiency in the performance of muscular work

may be increased somewhat in uncomplicated undernutrition (4). In realimentation, the specific dynamic effect of food may be exaggerated if the fat depots are rapidly replenished from the food supply. The vagueness of these statements indicates the lack of precise information on energy requirements in convalescence and the great need for comprehensive research in this field.

The realimentation of individuals convalescing from disease, or injury, or underfeeding would seem to be largely a matter of increasing the consumption of food energy from diets properly balanced with respect to protein, minerals and vitamins. To the extent that anorexia interferes with this plan, advantage may be taken of the sensation of thirst by resorting to the giving of nutrients in liquid form. In special cases, and under proper medical supervision, insulin injection may increase a lagging appetite. The use of vitamin preparations for this purpose, such as liver extracts, has been attended with some success. The success of Jokl and associates (13) in the rehabilitation of undernourished men by the institution of a regular prescribed system of physical exercises, accompanied by adequate nutrition, is impressive. Physical exercise, by its appetite-stimulating effect, may induce a consumption of palatable food in excess of that required to cover the increased energy expenditures and sufficient to induce an increase in body weight and well being.

In practical life, it is important to shorten the period of convalescence so that the patient can be returned as soon as possible to productive work. Successful realimentation, with high-caloric and well-balanced diets, is an important phase in attaining this objective, a phase that can be accomplished more successfully when more is known of the energy metabolism and the energy requirements in convalescence from diseases and injuries of various types. It is important also to follow the progress of convalescence in order to assess the success of the measures used in rehabilitation and in particular to detect the successful termination of the reparative period. Methods of measuring the physical fitness of the subject by observing the cardiovascular response to not-too-strenuous muscular exercise are available and should prove of service (cf. Taylor and Brozek in this Symposium). When the imposition of considerable muscular stress is inadvisable, other methods bearing upon energy transformations and efficiency of energy expenditures may be applicable. The shift toward normal in basal metabolism may be indicative. The creatinine output per unit of height or of body surface responds both to a shift toward normal in basal metabolism and to the reparative processes occurring in the muscles. The return of muscle tonus to a normal vigor may be revealed by picking up and measuring the action potential of the muscles at definite points on the body. The response of the cardiovascular system and of the intensity of the energy metabolism to changes in posture from the recumbent to the sitting or the standing position may reveal a return to normal health in a decreasing increment of response. The vital capacity has proved of value when applied repeatedly to the same patient in following the progress of pathological disturbances, and may be of some aid in manifesting the progress of convalescence.

All of these methods bear more or less directly upon the energy metabolism in convalescence. Disturbances in energy metabolism induced by disease and injury and the consequent bed confinement lead to an impairment in the voluntary uptake of food energy, to a depletion of energy reserves and a lowering in basal energy expenditures, and to muscular weakness and inefficiency. Therefore, in the rehabilitation of the convalescent an item of prime importance with few exceptions is the restoration of the energy metabolism to normal levels of performance and efficiency by realimentation based upon a knowledge of the damage inflicted.

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PROBLEMS OF NITROGEN METABOLISM

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It has long been recognized that patients with a variety of infectious diseases use protein extravagantly. Most early observers (1, 2, 3, 4, 5, 6, 7, 8, 9) agreed that the negative nitrogen balances regularly observed in these conditions could be alleviated, but not prevented, by large excesses of calories in the form of carbohydrate and fat. This gave rise to the general opinion that they were obligatory and unpreventable, which is reflected in the term, *toxic destruction of protein*. Excessive losses of nitrogen have been reported in a variety of other pathologic conditions: for example, after acute hemorrhage (10, 11), operations and injuries (12, 13, 14, 15), and in gastrointestinal obstruction (16, 17, 18). In many instances these losses can be attributed largely to starvation and inadequate feeding; in others to infection or to exudation.

Since protein is an essential constituent of tissues and cannot be replaced by other materials, those tissues from which it is withdrawn must presumably suffer some deterioration. The general deleterious effects of protein deficiency in diseased and injured subjects have been emphasized frequently (19). That famine edema arose from lack of protein in the diet was suggested (20, 21) before it was demonstrated by Kohman (22), whose observations have been amply confirmed (23, 24). Its relation to low serum protein was first suggested by Knack and Neumann (20). Since then it has been demonstrated abundantly that only the albumin fraction suffers depletion (24, 25, 26, 27). In the absence of hemoconcentration, reduction of serum albumin is a diagnostic sign of protein deficiency (25, 26, 27). Because the variation of albumin in normal serum is so great and because the plasma volume tends to contract as the concentration of albumin falls (24), there must be considerable depletion of protein before hypoalbuminemia becomes conspicuous.

Only a small part of the protein actually sacrificed in protein starvation is derived from the plasma. In a dog who received a protein-free diet for a long period, Weech et al (24) found that serum albumin accounted for only 3 per cent of the protein lost; 18 per cent came from hemoglobin; the great mass, about 80 per cent, was yielded by the tissues. This explains the large amounts of protein that are required to replace a serum protein deficit (28).

Studies upon the indispensability of amino acids, begun by Hopkins (29), Osborne and Mendel (30) and their associates, culminated in the demonstration by Rose (31) that animals can survive, maintain nitrogen equilibrium and grow on diets in which all protein must be derived from 10 amino acids. Although this has been questioned by Albanese and Irby (32), it has been confirmed by Madden et al (33) and Kinsey and Grant (34). The latter attribute the failure of Albanese and Irby to the administration of inadequate amounts of the 10 essential acids.

For parenteral injection mixtures of pure amino acids appear to have distinct advantages over less refined products. Madden (33) has shown that they can be injected in high concentration with great rapidity without provoking untoward reactions, and that they are removed from the blood promptly and utilized with economy. High prices and scarcity, however, prohibit the general use of such mixtures for clinical purposes. Hydrolysates of natural proteins are available. Hydrolysis by the conventional method with sulfuric acid and heat has been found to destroy a large proportion of certain amino acids, especially tryptophane and

cystine (or methionine) (35). This difficulty can be eliminated by conducting the hydrolysis with more dilute acid, especially if oxygen is excluded (36). As yet, however, no satisfactory acid hydrolysates are available. A satisfactory enzymatic hydrolysate of casein and pork pancreas is on the market (*FN*).[1] Properly prepared solutions of this material can be injected intravenously without inducing pyrogenic or other untoward reactions (37). It has been demonstrated that this preparation, injected intravenously, is, from the nutritive standpoint, an effective substitute for dietary protein (37, 38, 39, 40). The hydrolysate can be given orally, but is so unpalatable that for this mode of administration it has no especial advantages. It has been given by tube into the stomach or intestine in quantities exceeding the equivalent amounts of protein that patients could be induced to eat (14, 41). It is not certain, however, that preformed protein could not have been given in equivalent amounts by tube with equally good results.

In early studies the quantities of protein which could be given were limited by the appetites of patients and by the prevalent doctrine that large quantities of protein were injurious to sick persons. Therefore, although it was ascertained that toxic destruction of protein could not be prevented entirely by generous quantities of protein with large amounts of carbohydrate and fat, it was not determined whether the protein losses could be replaced by sufficiently large quantities of protein. The elimination of the old fear of protein and the presentation of protein hydrolysates suitable for parenteral use has permitted examination of this problem.

It has been shown by Elman (37, 37a)that losses of nitrogen usually observed in the first 10 days after abdominal operations can be largely or completely obviated by the administration of adequate amounts of protein supplemented by injections of protein hydrolysates and glucose. It is impossible, however, to determine how far this merely prevented the inroads of starvation and inadequate food. Cuthbertson (12), Howard (15) and others (42) have found that the nitrogen excretion on the day of a simple operation, despite almost complete starvation, is quite low. In the succeeding 3 days it rises to a level distinctly above that usually encountered in starvation, reaching a peak when the patient is taking a maximum diet, at which time the nitrogen balance remains negative. The duration of this protein destruction is, however, short; positive nitrogen balance with replacement of lost protein sets in early and the total loss of protein, if the diet is adequate, is small. In patients with fractures Howard (15) has reported for larger and longer negative nitrogen balances that are practically uninfluenced by raising calories and protein in the diet. A group of patients with fractures wasted nitrogen for an average of about 36 days, in which they lost altogether an average of more than 200 gm. of nitrogen, equivalent to 1400 gm. of protein, or 7 kg. of muscle. This phenomenon had been earlier noted by Cuthbertson (12). In certain acute infections, especially meningitis, Peters et al (42) have observed similar losses persisting for a considerable time after the acute phase of the disease had subsided. These were not abrogated even when, with the aid of parenteral protein hydrolysates, the intake of protein was increased, in one instance to 178 gm. per day. In fact the negative nitrogen balance was not perceptibly influenced by the protein intake.

Burns represent a special case because they are attended by profuse exudation of preformed protein from the denuded skin surfaces. Presumably this is more or less equivalent to the direct abstraction of protein from the serum. When plasma proteins are withdrawn by plasmapheresis it is possible to maintain nitrogen equilibrium and to prevent or mitigate hypoproteinemia by the administration of high grade protein (43, 44), or by injections of serum protein (43) amino acids or hydrolysates of protein (45). In nephritic patients with profuse albuminuria, the protein lost in the urine can be replaced, or at least nitrogen equilibrium or positive balances can be established, without difficulty (46, 47, 48). Reconstitution of serum proteins, on the other hand, is an extremely slow process. If the albuminuria is extreme, exceeding 10 to 15 gm. of protein per day, it is difficult, if not impossible to restore the serum albumin to normal. It may be that when serum albumin is withdrawn at a rapid rate in the preformed state the specific process by which it is manufactured becomes exhausted. Some support for this view may be found in the observations that the serum albumin of patients with profuse proteinuria and extreme hypoalbuminemia contain less than the usual amount of sulfur (49) and have lost their antigenic properties (50). Whether losses of preformed protein through other channels ever have the same effect has not been ascertained. In burns the exudation of protein seldom attains comparable magnitude and duration (41, 51).

In a series of patients with burns Cope et al. (52) were able to replace urinary nitrogen losses without difficulty when diets were taken containing moderately large amounts of protein and calories. Taylor and associates (53, 54), on the other hand, in 9 patients were unable to replace urinary nitrogen with high caloric diets containing 100 to 125 gm. of protein per day. They found as much as 45

[1] *FN: Amigen*, manufactured by Mead, Johnson and Company.

gm. of nitrogen in one day in the urine of one patient. Neither of these groups measured the nitrogen in the exudates from their patient. Co Tui et al. (41) produced positive nitrogen balances (estimated from urine and diet) in 3 severely burned patients by giving enormous quantities of protein and protein hydrolysates by stomach tube. Their positive balances must also be discounted because exudates were only incompletely analyzed in sporadic periods; but these could hardly have accounted for the large apparent storage. In one instance weight and serum albumin deficits did not rise until dietary protein was increased to 300 and 400 gm. per day, of which 200 and 250 gm. per day, respectively, were retained. The authors imply that these quantities of protein were required, but the urinary nitrogen figures in none of their cases indicate excessive nitrogen catabolism. The large retentions of protein can only mean that the patients had suffered antecedent protein depletion and were still wasting protein in their exudates. Browne (55)and Hirschfeld (51) and their associates, like Taylor and his group (53, 54), were unable to prevent loss of nitrogen in the urine, neglecting the extra discharge in exudates, in the period immediately following severe burns. Supplementary protein hydrolysate was altogether wasted (55). In later stages, when the patients were greatly undernourished, these burned patients, like Howard's (15) fracture cases and the reviewer's (42) subjects with acute infections, gradually came into nitrogen equilibrium and finally established positive balances. In this state, when they suffered renewed trauma or developed infections, some of Browne's (55) patients continued to store nitrogen. The impression is acquired that a healthy man subjected to acute infection or injury suffers protein depletion that cannot be prevented by any dietary measures thus far discovered. On the other hand, the subject who is malnourished and who has already been depleted of protein can summon certain conservative processes that permit him to utilize protein for the reconstruction of tissues. This may explain why Shaffer and Coleman (3) obtained nitrogen equilibrium during a typhoid relapse in a patient who had consistently a negative balance in earlier stages of the disease. It accounts for the comparative ease with which positive balances can be established in pulmonary tuberculosis (56) and in chronic infections (42). It may also explain the contradictory reports of protein metabolism in burns and operations. Success or failure in establishing positive nitrogen balances depends on the initial state of the subject. The unprecedented amounts of nitrogen retained by Co Tui's burned patients (41) and his patients with gastrointestinal operations (14) are themselves convincing evidence of antecedent protein depletion.

The significance of this accelerated protein catabolism after injury is not clear. That absorption of protein is unimpaired is attested by innumerable analyses of stools (1, 2, 3, 7, 15, 42). In any case impaired absorption could not explain excessive urinary nitrogen nor failure to utilize parenteral hydrolysates. The tradition that inactivity leads to atrophy of disuse is supported by no objective evidence. The literature is full of records of normal men who have been kept in nitrogen equilibrium in bed. Both Howard (15) and the author (42) have records of nitrogen equilibrium in preoperative periods of patients who had negative balances after operations. Howard (15) found that patients subjected to osteotomy wasted less nitrogen for a shorter time than those with traumatic fractures, although the limbs of both were equally immobilized and apparently atrophied to the same extent. The old concept of deposit protein, a moiety of carelessly expendable protein that plays a minor role in the physiological economy, has been much discredited in recent years. To revive it now is hardly appropriate since in this catabolic phase of injury exogenous protein seems to suffer the same degradation as endogenous. For the same reason the conception that the nitrogen losses are only a manifestation of destruction of tissue, local or general, under the influence of toxins or other noxious products is hardly satisfactory. Synthesis of protein seems to be in abeyance. Apparently perfectly good amino acids and other products are no longer used. The duration and the intensity of the inhibition appear to vary directly with the severity of the injury and to be inversely related to the state of nutrition.

The destruction of protein cannot be attributed merely to accelerated energy expenditure or heat production, since high caloric diets protect protein both in exercise (7) and in hyperthyroidism (8, 9, 57, 58). It is not related to the degree of febrile reaction. Graham and Poulton (59) found that nitrogen catabolism was not augmented by artificial fever induced by placing a subject in a hot box. Protein wastage was observed during recovery from meningococcus meningitis when the temperature was not elevated (42, while storage was obtained in febrile patients with chronic infections (42) and pulmonary tuberculosis (56).

It is conceivable that the course of protein metabolism is distorted after injury, perhaps that certain amino acids are diverted from their normal paths during the processes of repair. A few available analyses indicate that the extra urinary nitrogen is chiefly urea (7, 8, 12, 55). If the limiting factor were a particular amino acid it should be possible to break down the barrier to synthesis by increasing the quantity of protein given. Transfusions of whole blood by Cope (52) did not in-

crease urinary nitrogen. In one instance Browne (55) found that the protein of plasma infusions was retained, whereas the protein of hydrolysates was not. Blood and plasma in these circumstances, however, may have been used to replace specific deficiencies of blood elements, thereby evading the metabolic processes to which other proteins and amino acids were subjected. Neither blood nor plasma appear to be efficient sources of protein for general nutritive purposes, compared with hydrolysates of high class protein, although they specifically correct anemias and plasma protein deficits.

Howard (15) has made the curious observation that throughout the period of nitrogen loss potassium is stored. The positive balances are astonishingly large, in one case over 1300 millimols, equal to more than 20 per cent of the potassium in the total body fluids of a normal man.

It has been suggested that certain ketosteroids, since they promote protein synthesis, be used to combat the nitrogen wastage in disease (60). Increased urinary excretion of ketosteroids has been reported after injuries (51, 61). It has been claimed that testosterone will reduce urinary nitrogen in injured persons (60). The evidence is, however, conflicting (62). Differences may arise from failure to distinguish between the early destructive stage and the later anabolic stage.

It comes as something of a shock to learn that the proteins of the healthy person are more vulnerable than those of the wasted individual. It suggests that this wastage may be associated with the process of repair rather than the destruction arising from the initial injury. It may justly be inquired whether serious efforts should be made to feed large quantities of protein in the early catabolic stage of disease or after injury, if it is a nutritive futility. A definite answer to this question must wait upon further knowledge. It would, however, be unfortunate not to take advantage of the heightened synthetic powers in the subsequent reconstructive stage. So long as the point of transition cannot be determined by any simple method, it seems preferable to risk early extravagance which has no obvious deleterious effects, than to prolong parsimony into a period in which it may delay rehabilitation. Reason may be exercised in feeding. Administration of large excess of protein (more than 100 to 125 gm. daily) immediately after injury is not indicated until some means is found to circumvent its immediate destruction; but throughout disease to provide generous supplies of food with adequate protein will insure against prolongation of malnutrition. The destructive phase of protein metabolism appears to vary with the severity of the injury (12, 15). After simple operations, minor traumatic insults or infections nitrogen losses may be minimized and restoration accelerated by early generous feeding. The initially debilitated individual certainly deserves vigorous administration of protein and calories from the first because his capacity to utilize protein for the reconstitution of his tissues does not seem to be impaired.

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BONE METABOLISM

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A résumé of all knowledge of bone metabolism which might conceivably have some bearing on problems of convalescence, entirely aside from its burdensome length, would be difficult to prepare on account of the numerous disagreements in the literature. Furthermore, many of the investigations have given results which are applicable only in special and restricted circumstances or refer to conditions which can be produced only in animals under experimental conditions. If, on the other hand, the discussion were confined to matters of proven clinical usefulness, only a very limited set of indefinite recommendations could be offered. The only useful function which this review can serve is to describe the needs for further explorations in this field and to indicate, in some cases, the methods by which the information might be sought. An attempt will be made to treat in some degree the following topics: (a) General metabolic consequences of fractures, (b) Factors influencing fracture healing, and (c) Disuse atrophy of the skeleton.

Metabolic consequences of fracture. In spite of a very considerably body of evidence for a contrary opinion, the mature skeleton was frequently regarded as being outside the pale of metabolism until the studies employing radio-active isotopes presented direct proof of the constantly occurring exchange of the elements of the bone salt. If the metabolic activity of bone is recognized, it follows as a natural consequence that the skeleton can suffer deleterious effects as a result of changes from the normal of those factors which influence bone. While the metabolically induced alterations of mature bone are, in general, produced at a comparatively slow rate, these changes may become of consequence during a prolonged convalescence from disease or injury. The fact that bone exhibits a metabolic activity has another corollary; namely, that trauma or infection primarily affect-

ing bone may also induce alterations in the metabolism of extra-skeletal tissues.

Cuthbertson (1) investigated the disturbances of metabolism produced by fractures of the bones of the limbs and found an approximate correlation of the extent of the heightened metabolism with the severity of the lesion. After an initial period of depressed function immediately following the fracture in which the heat production and body temperature were diminished, there occurred a period of increased metabolic activity. In the latter period, of variable length with individual patients but lasting several days, there was an increased basal consumption of oxygen and an elevation of body temperature. Coincident in onset and paralleling in time the increased oxygen consumption, there was a considerably increased excretion of urinary nitrogen. The maximum output of nitrogen usually occurred during the fourth to eighth day following the injury and then slowly declined. In one case the total loss of nitrogen over a ten day period was 137 grams, a quantity which was stated to be equivalent to 7.7 per cent of the total body nitrogen. Accompanying the increased rate of metabolism and augmentation of nitrogen excretion was an increased urinary output of sulphur, phosphorus, and to a lesser extent, potassium (2). The excretion of sodium was little affected and the creatinuria which developed and paralleled the rise in total nitrogen excretion was accompanied by little change in creatinine output. It was Cuthbertson's impression that the wasting of muscle and bone caused by immobilization of the limb was a contributory factor to the heightened catabolic phenomena but not their sole cause (2). The fever in itself was not believed to be the primary cause of the metabolic disturbances since it rarely exceeded 2°C. above normal temperature and because cases of pneumonia observed before and after the crisis failed to exhibit catabolic effects in excess of those noted in severe injuries to the limbs. Cuthbertson (2) attempted to influence the negative nitrogen balance of fracture cases by adding to the basal diet, which contained sufficient protein for the nutrition of the normal adult, meat extracts (Bovril), amino acids (glycine and l-cystine), and proteins (gelatin and sodium caseinate). By increasing the daily nitrogen intake to the order of thirty grams through the addition of sodium caseinate to a basal diet of high caloric value, some reduction in the negative balance was observed. However, at the height of the catabolic disturbance even these diets failed to prevent the loss of body protein.

Cuthbertson (3) has also investigated the influence of massage and passive movements of the injured limb on the nitrogen excretion of both adult and young fracture patients. Four persons aged 34 to 59 years received such treatments applied daily for twenty minute periods beginning relatively late in the period of convalescence (18th to 46th day following the fracture). The daily nitrogen excretion was reduced by 0.55 to 2.62 grams beginning almost immediately following the institution of the physical therapy measures. It is not clear what the nitrogen balance of these patients was at the time the treatments were started. However, in the case of normal uninjured adults (4) no such effect, produced by massage, on nitrogen excretion was observed. It can, therefore, be presumed that the results obtained by Cuthbertson with the fracture cases were in some way associated with the metabolic state of these individuals or that the physical therapy measures influenced nitrogen retention in the injured limb. Some indication was also obtained that an increased retention of sulphur and phosphorus resulted from massage and passive movement of an injured limb. These observations indicate the need for further investigations, employing complete balance studies, of the influence of massage and other physical measures on the excessive catabolism of fracture cases. It should also be determined how early in the period of convalescence these effects can be produced. It is, of course, already recognized that physical therapy is a valuable adjunct in the convalescent treatment of fractures of long bones and of serious injuries to the soft tissues of the limb, since these forms of treatment contribute to an earlier and more complete recovery of function of the injured limb. However, if it should turn out that an important reduction in the catabolic disturbance could be effected by massage and that this result is of benefit to the patient, added emphasis would be directed to the desirability of planning the treatment of each case so as to allow the earliest possible use of the methods of physical medicine.

There was some suggestion from the relations of the quantities of extra output of nitrogen, sulphur, phosphorus, and potassium in the urine of fracture patients that muscle and probably bone were being catabolized (1). This point was more directly investigated by employing rats which were sacrificed ten days following an experimentally produced comminuted fracture of one femur (5). The lesser weight of the injured limb was insufficient to account for the total weight loss of the animals and the nitrogen lost from the muscles of the injured limbs (calculated from the weight lost by the limb and the nitrogen content of muscle) was only a small fraction of the total nitrogen lost by the entire organism. It thus appears that protein tissue other than that in the affected extremity contributes to the extra output of nitrogen. About four-fifths of the observed weight loss of the animals, averaging 17 grams, could be accounted for by assuming that the excess

nitrogen output was derived from catabolized muscle. The remainder of the weight lost was presumably derived from the reserves of carbohydrate and fat. These animals were fed a diet which was just sufficient to maintain body weight before the injury. When this diet, supplied to animals with fractured femora, was supplemented with cane sugar fed *ad libitum*, the initial body weight was almost retained and the animals ended the ten day period with a slight gain in nitrogen over that lost in the excreta. The atrophy of the muscles of the injured limb was reduced to some measure but was not completely prevented by the dietary carbohydrate supplements. It thus appears that nitrogen may be lost from two general sources during convalescence from fracture: (1) A general increase in protein catabolism of the tissues accounting for the major loss of nitrogen, and (2) Autolysis at the site of injury and atrophy of the uninjured muscles of the fractured limb. The authors of the paper under discussion recommended as good clinical practice the feeding of the maximum possible intake of energy producing foods to injured patients as a means of sparing the catabolism of the tissue proteins which would otherwise occur.

Howard and his co-workers have carried out extensive balance studies with fracture cases.[1] These observations permit further definition of the extent and time relations of the metabolic disturbances of convalescent fracture patients. Even though the collections could not be started for three days to one week following the injury, the average amount of nitrogen lost by five patients before nitrogen equilibrium was established was 189 grams. The average duration of the period of negative nitrogen balance was 33.6 days and the maximum rate of protein catabolism was usually observed to occur within the first week following injury.

Howard's investigations demonstrated a catabolic disturbance of fracture patients which was not observed by Cuthbertson, namely that a very considerable negative calcium balance also occurs. The urinary calcium excretion rose gradually as the rate of nitrogen excretion fell and reached its maximum only after the third to fifth week following the injury. This maximum excretion of calcium was thereafter maintained for several weeks and varied between 350 and 800 mg. per day among the individual patients. Because of the appearance of the charted data, the period of constancy of increased calcium output is referred to as the "plateau of calcium excretion." The influence of factors which might affect calcium excretion and balance was studied in several patients after they had been observed to enter the plateau of excretion of this element. By increasing the calcium content of the basal diet from a daily intake of 250 mg. to an intake of two grams, several patients were put into a state of positive calcium balance, or the negative calcium balance was very much lessened. This saving of calcium to the organism by high intakes of the element was secured with only slight increases in urinary calcium excretion. This last observation would appear to indicate that the feeding of diets high in calcium would not contribute to the formation of renal calculi in patients immobilized for the treatment of fractures. The effect of high calcium intakes in converting the state of negative balance to one of essential equilibrium was obtained whether the calcium was supplied either in the form of milk or calcium lactate. There was no evidence which could be secured in these investigations as to whether the calcium stored on the high calcium intakes contributed in any way to the bony union of the fracture.

Howard has continued his balance studies for a considerable time after nitrogen equilibrium was established and has noted that the protein lost during the period of negative nitrogen balance is only slowly recovered. Even though the patients ingested 110 grams of protein in a daily diet of 2800–3000 total calories, they recovered, in a period of upwards of sixty days, only about thirty grams of approximately 200 grams of nitrogen which they had lost.

The metabolic effects described above are not unique to fracture cases as practically all are seen, although perhaps modified in degree, in other severe traumatic injuries and in many debilitated states. The important point of reference is that these effects do occur in recovery from skeletal injuries. Their influence on the healing process and their relation to the general physiological welfare of the patient have not been assessed. Munro and Cuthbertson (6) found that nitrogen starved rats did not exhibit an increased nitrogen excretion following fracture. These authors were, therefore, inclined to the belief that the excessive output of nitrogen following injury of a normally fed animal arises from storage protein and not from essential body tissues. Howard[1] has noted, in the case of a patient whose protein intake was very low, a result very similar to that observed by Munro and Cuthbertson. Even if the "deposit protein" is the source of the excreted nitrogen, a

[1] This work has been described in a preliminary fashion in the minutes of the 2d, 3d and 5th meetings of the Conferences on Metabolic Aspects of Convalescence Including Bone and Wound Healing sponsored by the Josiah Macy Jr. Foundation. These minutes have had only a restricted circulation and for the present are of the nature of a personal communication. Dr. John E. Howard has given this writer permission to refer to his work.

supposition which is not entirely proved, there is no assurance that the depletion of the more labile body proteins is without influence on the welfare of the patient.

Roche and his co-workers have described the osseous system as acting as a physiological unit. In animals a general increase of the phosphatase activity of the skeleton was noted after the fracture of one bone. The corresponding intact bone of the opposite side showed the same chemical changes of decalcification and recalcification as the fractured bone but to a lesser extent (7).

Fracture healing. A description, differing in some major respects from the older concepts, of the process of fracture healing in man has been given by Urist and Johnson (8). Their material for study was the biopsies taken at various times after the injury of forty-eight cases of normally healing fractures. This process consists essentially of the following successive stages: (1) The *pro-callus* which is the organizing hematoma and highly vascular granulation tissue, (2) The *fibrocartilaginous callus*—a translucent mass of dense fibrous connective tissue, fibrocartilage and cartilage derived from the undifferentiated connective tissue cells, and (3) The *bony callus*. The bony callus first makes its appearance on the endosteal and subperiosteal surfaces of the fracture ends and advances to bridge the fracture gap by replacing the fibrocartilaginous callus.

Utilizing methods which permit, in young or rachitic animals, the sectioning for microscopic study of undecalcified bone, Urist and McLean (9) studied the processes of fracture healing in rats. In normally fed animals the bone matrix which replaces the fibrocartilaginous callus calcifies as rapidly as it is formed. In rachitic animals, as a result of a disturbance of the calcification mechanism, the matrix remains uncalcified for a time. It is therefore to be emphasized that the appearance of what has been referred to as "physiological osteoid" is a result of sub-optimal conditions for fracture calcification. The healing of fractures in rachitic rats is further complicated by encapsulation of the callus cartilage in a dense mass of fibrous tissue or fibrocartilage which forms a barrier to the advance of uncalcified osseous tissue. In man, in contrast to normal rats and presumably other lower animals, a lag in the calcification of the matrix is the rule rather than the exception. This delay of calcification may be attributed to a rate of osteogensis greater than the rate at which the calcification mechanism can operate at the low level of serum phosphate in all individuals except infants and very young children.

When rachitic rats bearing a fracture were treated by a single parenteral administration of a phosphate solution, prompt calcification of the osteoid of the callus was initiated provided the interval of time between the fracture and the phosphate treatment was not sufficient for the barrier of fibrous tissue to develop about the callus (9). In the latter case, a delay of some days in the initiation of calcification of the callus cartilage occurred even with repeated administrations of phosphate.

These observations are quite clear in demonstrating that disturbances and delay of fracture healing may result from deficiencies of the calcification mechanism, and they may have some bearing on problems of delayed union and non-union of fractures in man. It would appear that the logical attack on these problems should be begun early following the injury in an effort to prevent the alterations of callus structure which follow delay in calcification. If the more feeble mechanism for calcification possessed by the adult human, in contrast to that of young children, infants and the rat, is in fact due to the lower inorganic phosphate of the plasma, an obvious way to correct the deficiency of the adult would be suggested, namely phosphate therapy. Somewhat against the probability of success attending phosphate administration is another observation of Urist and McLean (9). They found that fractures of adult rats which had been fed for ten weeks on a rachitogenic diet previous to the injury healed with only a slight lag in the calcification of the callus. In these animals, minerals mobilized from the skeleton were sufficient to provide for bony union at a normal rate.

Since the various forms of the provisional callus and its matured form, the calcifiable matrix, are composed of proteins it is conceivable that delay of fracture healing may be related to quantitative or qualitative disturbances of protein anabolism. From a clinical viewpoint, the consolidation of the fracture is a valuable criterion for arriving at a judgment as to when the fractured bone may be returned to function. Some fracture surgeons express the opinion that clinical consolidation is determined to an important degree by firm soft tissue union since roentgenograms frequently fail to show demonstrable bony callus when consolidation is present. Nevertheless, it is probable that union can be considered to be present only when newly deposited bony callus (compact bone and spongiosa) repairs the defect in the shaft (8). The similarity of density of the newly deposited bony callus and a thick layer of muscle accounts for the frequent failure to visualize the partially and newly calcified callus on clinical roentgenograms.

If some recognized or subtle alteration of protin metabolism should prevent or delay the series of changes in the soft callus preliminary to the development of the matrix, union would be interfered with to a proportionate degree. While these

factors should be given some consideration, it appears that very severe modifications of the protein stores are required to interfere with fracture healing. Rhoads and Kasinskas (10) by lowering and maintaining the plasma protein level of dogs to approximately 4.0 grams per 100 cc by repeated plasmapheresis, produced a definite retardation in the formation of the bony callus in defects in the ulnae.

The literature of clinical medicine describes numerous claims for methods to improve the rate of fracture healing by medical methods (as adjuncts to the surgical methods of reduction and immobilization). However, the great variety of circumstances attending fractures and their healing in the human, the near impossibility of the control of many of these factors in patients, as well as the fact that the results must be estimated by non-objective means have prevented adequate evaluation of any of the proposals for improving the medical management of fractures. Certainly it is fair to conclude that the results have not been sufficiently impressive to cause any of these methods to be accepted as of demonstrable value in the regimen of fracture therapy in other than the exceptional case. Studies with experimental animals have likewise not been fruitful in producing any therapy which accelerates the healing of fractures in normal animals fed an adequate diet. No proven correlations of the content of serum calcium, inorganic phosphorus, or alkaline phosphatase activity with delay in fracture calcification in the adult human (8) or normally fed experimental animals have been demonstrated. Mention has been made above to the effect that the lower normal inorganic phosphorus of the plasma of adults may be related to the more feeble ability of adults, in contrast to young children and rats, to calcify the fracture callus. It may be mentioned in this connection that the delay in calcification of the matrix in rachitic rats has been correlated with the lowered plasma inorganic phosphorus (11).

The fact that nothing of demonstrated worth for influencing the healing of the usual fracture has been discovered does not prove that this is an impossible task or justify a complacency in the acceptance of the belief that a certain time, as determined from the observation of previous similar cases, is required for the union of a given fracture of a particular bone. If the period of healing of the average fracture case could be reduced by even ten per cent a very appreciable saving in the period of hospitalization and the benefits of an earlier return to function of the injured bone would result.

For reasons mentioned above, it does not appear likely that methods for the improvement of fracture healing can be systematically investigated in the human. Although it might appear that these problems could be easily attacked using experimental animals, a number of difficulties of procedure and interpretation of results are experienced. An acceptable method for use in the investigation of factors influencing fracture healing must satisfy at least the following requirements: (a) a uniform lesion must be produced among the several animals, and (b) the degree of healing must be determined by objective methods. Most of the studies which have been reported have employed methods which have failed to satisfy one or both of these requirements. Some consideration must be given to what is meant by fracture healing. An important clinical criterion is sufficient consolidation of the fragments to allow use of the bone. If it be accepted that consolidation or union is conditioned by the degree of calcified tissue bridging the fracture defect, a determination of the state of calcification of the callus would furnish one quantitative method for defining the state of experimental fracture healing. Direct estimations of the degree of consolidation have been carried out by measuring the resistance of the fractured bone to deformation about the fractured site by bending, torsion, and tensile forces, and by determining the force required to refracture the bone. One group of workers employing these methods used the rat fibula (12) which is fused at its lower end to the tibia and another group the rabbit ulna (13). The rat fibula and one of the two forearm bones of other animals are convenient for the study of fracture healing since no splints or other apparatus are required to hold the fragments in apposition and alignment.

The production of a uniform and reproducible fracture defect practically requires that it be produced by open operation. Some investigators have cut or broken the rat fibula (12), (15) or the ulna (13) or radius (14) of other animals or removed a segment of the ulna (10). Bourne (16) drilled a small hole through one cortex of the rat femur and determined the degree of healing by estimating the relative area of bone trabeculae in sections cut through the healing lesion and prepared for microscopic examination.

This writer has used lesions prepared by trephining a three-sixteenth inch hole through the entire shaft of the humerus of the dog (17). At this operation a biopsy of the bone practically equivalent to the entire volume of bony defect is obtained. After an arbitrarily chosen period of twenty-one days, during which one or another experimental regimen is applied, the animals are sacrificed. The entire contents of the hole are removed with the same instrument as was used in the production of the defect. The total quantities of calcium, phosphorus and nitrogen are determined in the biopsy and in the partially healed

bony defect. The degree of healing is described in terms of the amounts of each of these three elements found in the healing lesion as a fraction of the quantities of the same elements in the biopsy. A very considerable variation in the degree of healing, as denoted by calcification, has been observed among individual animals fed the same diet. However, when this type of experimental fracture is produced in each humerus of the same dog at one operative session, the degree of healing, as defined above, observed in the two bones has usually agreed within a much smaller variation than is noted among the various animals. It thus appears that some systemically operating factor is responsible in some measure for the degree of calcification of the callus and accounts for the variation of the results among individual animals. This factor which determines the degree of calcification is not related to the dietary intake of minerals or protein since the animals were fed a uniform adequate diet in an amount in proportion to their body weight. Furthermore, essentially the same results were obtained when the animals were fed diets with the calcium present in various states of combination or when the diets were practically devoid of this element. What results would be obtained under conditions of other or multiple dietary deficiencies, or with healing periods longer than twenty-one days, have not been determined.

Disuse atrophy. Atrophy of bone in the adult is manifested by a general wasting of the cancellous trabeculae and cortex of the involved bones. The volume and size of the bone and its composition with respect to the proportions of mineral and organic phases are not altered from the normal (18, 19); bone atrophy is in fact osteoporosis. The atrophy may be local or generalized and when generalized may result, among other causes, from inadequate intakes or from faulty absorption of calcium and phosphorus, from ammonium chloride acidosis, or parathormone injection. Marked degrees of atrophy are difficult to produce in adult animals by deficient intakes of calcium. The bones of adult rats fed for 220 days on a diet containing 0.007 per cent calcium and free of vitamin D suffered a reduction of only ten per cent in the contents of calcium and phosphorus per unit volume of bone (19).

In addition to other causes, atrophy of a part of the skeleton occurs as an accompaniment of disuse following paralysis or immobilization of a limb. This type of bone atrophy may be marked since it is frequently observed on clinical roentgenograms and it occurs in bones which, although not injured, are immobilized incidental to the treatment of a fracture of another bone. Whether significant degrees of skeletal atrophy can result from prolonged rest in bed or from inactivity due to debilitating disease has not been described. The cause of disuse atrophy of the skeleton has not been explained, although it is probably a condition in which bone formation fails to keep pace with bone resorption. In this connection the high rate of urinary calcium excretion and negative calcium balance of fracture patients observed by Howard *et al.* may be recalled. This circumstance might be expected to accentuate the degree of disuse atrophy produced by immobilization.

No very great clinical significance has been attached to ordinary degrees of disuse atrophy. It has recently been reported that biopsies of fractures of ambulatory patients showed about the same quantity of uncalcified osteoid as those of partially or totally immobilized patients (8).

Disuse atrophy of the humerus in the rat

GROUP	TREATMENT	NUMBER OF ANIMALS	DIFFERENCE IN WEIGHT OF HUMERI MEAN ± S.D.	DIFFERENCE IN ASH WEIGHT OF HUMERI MEAN ± S.D.	DIFFERENCE IN ASH WEIGHT OF HUMERI MEAN ± S.D.
			grams	*grams*	*per cent*
A	Unilateral Section Nerves Brachial Plexus—Controls	33	0.0189±0.0077	0.0135±0.0055	8.75±3.55
B	Same as A plus orchidectomy	20	0.0248±0.0081	0.0184±0.0062	15.96±5.47
C	Same as A plus 5 mg. testosterone propionate daily	10	0.0172±0.0053	0.0120±0.0038	8.39±3.18
	Same as A plus 50 gamma estradiol dipropionate each alternate day	23	0.0083±0.0036	0.0067±0.0022	4.21±1.82

It was concluded that increased excretion of calcium, associated with immobilization or atrophy of bone, is not responsible for the delay of calcification of the callus in man. However, these ambulatory patients all bore casts so that the factor of disuse atrophy was present in at least the healing bone. Fractures of rabbits in which skeletal atrophy was produced by starvation were retarded in healing and the mineral phase which was first laid down was later absorbed (20). However, in young rats bony atrophy caused by low calcium intake was accompanied by essentially normal fracture healing (18).

A simple and adequate means for the investigation of factors influencing disuse atrophy caused by paralysis in the mature rat is available (21). The nerves of the brachial plexus are sectioned unilaterally in the axilla. After an arbitrarily chosen

period of twenty-one days following this operation the animals are sacrificed. The dry, fat-free weight and ash weight of the humerus of the paralyzed arm are compared with the corresponding figures pertaining to the humerus of the normal limb. It was demonstrated in confirmation of previous work (22) that no significant differences of weight or ash content exist between the right and left humeri of normal, unoperated rats. Table I presents some selected data which have been obtained in this study of disuse atrophy. If the not inconceivable assumption is made that some of the factors which affect disuse atrophy might have an influence on fracture healing this method might be of use in a search for forms of therapy to accelerate the latter process.

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VITAMIN NUTRITION IN CONVALESCENCE AND REHABILITATION

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Diet has always held a prominent place in programs for convalescence and it would be expected that modern knowledge of the vitamins should have important applications in this field. Detailed data are not available but it is certain that vitamins, either prescribed or self-selected, are widely used by patients whose primary disease has run its course or has been arrested.

The potential importance of the subject need not be gauged by the fact that the current interest in vitamins has produced remarkably little acceptable evidence for their clinical value except in conditions of definite avitaminosis. The present discussion is intended to examine the rationale for special attention to vitamins in convalescence and to clarify the needs for critical researches. Space does not allow discussion of neoplasms, virus infections, pregnancy and lactation or the special problems of infancy and childhood. Only passing reference can be made to vitamin deficiency in the pathogenesis of disease (132).

Obviously any convalescence program should provide for the immediate correction of any existing vitamin deficiencies and ensure that subsequent deficiency does not develop. Frank deficiencies should be recognized readily. The real problems have to do with the recognition of deficiency in the complicating presence of other

disease, the provision of vitamins which may be needed in the repair of disease or injury, the compensation for defects in metabolism or absorption of vitamins, the possible enhancement of resistance to infection, and provision for possible special requirements to allow maximal restoration of "fitness" in the patient.

It is essential at the outset to differentiate between the clinical and the scientific problems. Practices which are little supported by valid scientific data may be justifiable from the viewpoint of clinical conservatism. If there is no obvious risk or difficulty in administering large dosages of vitamins then it may be argued that these should be prescribed without proof of their utility. Much is made of this reasoning by some enthusiasts. On the other hand, the indiscriminate advocacy of "shotgun" vitamin supplementation discourages discovery of specific needs and may defeat its own purpose because of the practical impossibility of applying massive general vitamin supplementation to all patients. There is another aspect. It is not impossible that high dosages of vitamins may produce metabolic alterations which are not adapted to the specific repair processes in disease. Thought should be given also to the possible acceleration by superabundant vitamin supply of degenerative changes and the support of the metabolism of invading microorganisms.

There is a dangerous tendency to facile reasoning from experience with frank vitamin deficiency disease. The common complaints of the convalescent—weakness, anorexia, depression, constipation, "nervousness"—have their counterparts in one or another avitaminosis but their treatment by similar therapy on this ground alone is not warranted.

General functions of the vitamins. In general, vitamins function as essential components of enzyme systems or of the physico-chemical architecture of living cells. It would be expected, then, that the requirements would be related, respectively, to the kind and intensity of the metabolism, or to the kind and amount of tissue to be maintained or formed. Some members of the B complex are known to be involved in energy metabolism while vitamins A and D are more specifically related to tissue growth. Accordingly it might be suggested that the needs of the convalescent could be estimated for categories of vitamins from a consideration of the purely metabolic needs, on the one hand, and the needs for new cell formation on the other.

Clear differentiation between enzymatic and structural functions cannot be established, however. The living cell is undoubtedly dependent on enzymatic reactions for the maintenance of its structure. From chemical considerations it must be believed, for example, that ascorbic acid significantly participates in metabolic reactions but its specific place in collagen formation suggests a primary structural function.

The fact that different tissues of the body normally exhibit characteristic differences in their content and dependence on the several vitamins raises several questions. Should the convalescent who has suffered damage to particular organs receive supplements of the vitamins in proportion to their normal concentrations in those organs? Or should therapy with specific vitamins be instituted for lesions involving particular organs or functions because these are especially susceptible to damage in the absence of those vitamins? It must be realized that the rationale of vitamin administration in disease has apparently been based on such ideas in many instances.

There is no acceptable evidence that healing and regenerative processes in general are expedited by large supplies of vitamins except where there has been previous definite deficiency. Indeed, it is remarkable that only severe states of deficiency seem to exert markedly adverse effects on such processes. We must conclude at present that simple new tissue growth makes no extraordinary demands for vitamins.

A distinction between the presumed different functional destination of the several vitamins has been recognized in recent recommendations for vitamin intake, including those of the National Research Council (89, 99). The recommended intakes of thiamine, riboflavin and niacin are roughly in proportion to estimated metabolism, whereas those of vitamin A and ascorbic acid are related more to body size, i.e., to the mass of living tissue. There are no authoritative recommendations for vitamin intakes in convalescence.

General bases for vitamin administration. The evaluation of the vitamin nutritional status in the individual is fraught with difficulty. Laboratory analytical methods, except for ascorbic acid and vitamin K (prothrombin time), are too cumbersome for routine application at present and in many cases the interpretation of results is still debatable (130) (80) (53). Special examination and test measures in general have not fulfilled early hopes. We may mention dark adaptation for vitamin A, corneal microscopy for riboflavin and capillary fragility for ascorbic acid. These methods are not reliable for detecting mild or early deficiency though they are useful on occasion.

Careful examination for clinical signs of deficiency should be applied to all convalescents. The nutritional history, including evidence of poor absorption, should be reconstructed as accurately as possible. The presence or a history of jaundice, biliary drainage or acholic stools suggest probable poor absorption of the fat-soluble vitamins. Severe

diarrhea may cause alterations of vitamin synthesis by bacteria in the intestine as well as seriously reduce intestinal absorption of all of the vitamins. Vitamin supplementation is indicated when any of these conditions is associated with suggestions of deficiency from laboratory or clinical findings.

Treatment of intestinal infections with sulfaguanidine and similar drugs may result in vitamin deficiency owing to interference with intestinal synthesis; the effect on biotin may be particularly marked (67). Other drugs may affect the net supply or metabolism of vitamins. The action of salicylates may not be an isolated instance. Salicylates increase the urinary excretion of ascorbic acid (106) and of thiamine (24), but it is probably more important that they interfere with the formation of prothrombin from vitamin K (68). This action of salicylates is potentially important because of their extensive use in diseases characterized by a long course or slow convalescence such as rheumatic fever, arthritis, malaria, and gout.

Few generalizations may be made about the effects of fever, infection or simple inanition. Infection even without fever or gastro-intestinal disorder, may greatly diminish the absorption of vitamin A and carotene (113). Effects of fever on vitamin A, thiamine and especially ascorbic acid are inferred from analyses of blood and excreta but the full significance of the alterations is not clear. There are bold assumptions in calculations that fever may destroy 100 mg. or more of ascorbic acid daily (37). Simple inanition alone does not seem to produce vitamin deficiency but little is known about the vitamin requirements for subsequent rebuilding of the tissues.

It should be obvious that, in general, the prescription of vitamins for convalescents at present must be largely dependent upon informed clinical judgment. Conservatism here consists in supplying vitamins in case of doubt, though we agree with Stare (115) that there is at present no rational basis for "overdose" therapy. The special needs for vitamins during and after particular diseases or injury remain to be discovered. Some considerations applying to the individual vitamins follow.

Vitamin A. Vitamin A is of interest in convalescence because of its role in tissue growth, its suggested importance in infection, the claims for its special benefit in certain chronic conditions and expecially because of the frequency of its inefficient absorption. Like the other vitamins it has received infinite but unwarranted praise for prophylaxis and therapy (23) (10) (18) (17).

The body reserves of vitamin A, chiefly in the liver, are ordinarily large. Extreme dietary deficiency is usually inconsequential for months in normals if the previous diet has been good (116) (123). However, a long course of disease and convalescence may result in deficiency which is correspondingly slow to correct. While it is important to maintain a good dietary intake, the greatest danger in convalescence seems to be poor absorption, particularly of carotene. Losses in the urine occur rarely in some diseases but these are never large (66).

Deficiency of vitamin A is very common in liver-disease and jaundice but bile salts are not important for the absorption of vitamin A though carotene may be more affected (65) (17). The low level of vitamin A in hepatitis and hepatic insufficiency is related primarily to faulty liver metabolism—impaired conversion of carotene to vitamin A (43), impounding vitamin A in areas of degeneration (96) or destruction by the deranged liver.

The fat solubility of vitamin A and carotene influences their absorption, which seems to involve association with fatty acids in the intestinal wall. Low-fat diets may hinder absorption but there are discrepancies in the evidence (87) (104). Lecithin improves vitamin A absorption even in colitis patients (4). Mineral oil interferes with the absorption of carotene by carrying it through the tract in physical solution. Diarrheas of all types, particularly steatorrhea, promote the loss of vitamin A and carotene in the feces. Vitamin A deficiency is not uncommon in these conditions (41).

The effect of vitamin A in relation to infection appears to have been overemphasized. Large dosages of vitamin A have little or no value in acute infection (21) (22) (110) and vitamin A supplementation to normals seems to have no effect on susceptibility to upper respiratory infections (111) (25). Important immunological reactions are not influenced by moderate degrees of vitamin A deficiency (39). Lowered resistance to infections occurs during and perhaps after severe vitamin A deficiency (12), but this may be related to secondary morphological changes; in any case concurrent nutritional deficiencies have not been ruled out. The level of vitamin A in liver and other tissues is very low in septic deaths (86) and the blood level promptly falls in infections in general (23). The cause of these effects is not clear but poor absorption does not explain the changes in acute conditions.

In tuberculosis the level of vitamin A in blood and tissues is low and relatively unresponsive to large doses of the vitamin (15). The fact that tubercular patients with pronounced gastro-intestinal symptoms exhibit the lowest levels suggests faulty absorption but general differences in the extent and severity of the infection may be responsible (73).

The occurrence of central nervous system

changes in children with keratomalacia is now agreed to be a secondary result of prolonged vitamin A deficiency. Mechanical pressure results from disproportionate rates of growth of brain and cranium (77) (78). The deficiency apparently retards bone growth more quickly than that of the nervous tissue (127).

Enthusiasm for the use of vitamin A in the local treatment of burns and other wounds has collapsed for lack of acceptable support. The more recent advocacy for this vitamin in hypertension is likewise unwarranted though further studies may be desirable in view of evidence for an effect on renal blood flow (122) (119). Claims for vitamin A in color blindness are denied (35).

The evaluation of vitamin A nutritional status has not been simplified by recent work. Xerophthalmia and keratomalacia are probably late developments in vitamin A deficiency. Dark adaptation tests increasingly appear to be non-specific and untrustworthy for diagnosis (31, 45, 117). Blood analyses for vitamin A and carotene are valuable but the relation between blood and tissue vitamin A is not always close and the methods for such chemical analysis are difficult. As with other vitamins clinical judgment is very important in practical work.

For the great majority of convalescents it appears that a good diet with plenty of butterfat and yellow vegetables will provide ample vitamin A. Where there are signs or a reasonable suspicion of past, present or impending A deficiency the question of dosage is raised. Vitamin A is to be preferred to carotene, especially in disease. Many investigators have used huge doses with success but daily parenteral doses of as much as 150,000 U.S.P. units for weeks may not improve the plasma level in hepatic insufficiency (1, 95, 97). The fact that months are required for healing in hyperkeratosis even with daily doses of 50,000 to 300,000 units does not mean that such large amounts are needed or useful; these processes of anatomical repair are inherently slow. A daily supply of 15,000 units has been reported to be just as effective as much larger doses in children with vitamin A deficiency (107).

The water-soluble vitamins. In clinical studies the water-soluble vitamins, particularly the B complex, are often involved as a group. The common factor of water solubility justifies consideration of the group as a whole with regard to absorption and excretion. The major members of the group likewise share the common property of participating in enzymatic metabolism or exhibiting high chemical reactivity.

The present National Research Council (89) recommended allowances for these vitamins have provoked some criticism as being unnecessarily high. The question of allowances for the sick and convalescent is still more controversial. The physician is rightly concerned with the necessity for speeding the recovery of the patient. In most cases vitamins are administered as an adjunct to other therapy so it is not surprising to find disagreement in clinical reports. Valid controls are usually absent. Physician and patient alike have been so conditioned by current propaganda for water-soluble vitamins that phychological artifacts may obscure any physiological phenomena.

The requirements for water-soluble vitamins are complicated by the contribution of bacterial synthesis in the intestine. This source of supply is so important that one or another animal species is relatively independent of the intake in food of thiamine, ascorbic acid and niacin. The facts in man are unknown except that some thiamine may be so provided (88). In any case residual peculiarities in the intestinal flora may increase the need for vitamin administration to some convalescents. Gastro-intestinal disorders and diarrhea appear to interfere less with the net absorption of water-soluble vitamins than with the fat-soluble group. These questions need much further study.

There is an increasing tendency to evaluate the nutritional status in the water-soluble vitamins from the urinary excretion. The arbitrary levels suggested to indicate adequacy are subject to serious argument (80, 60, 61). The concept of tissue saturation for adequacy is opposed by the theory that any perceptible excretion of the B vitamins in the fasting state indicates the absence of deficiency (53). Supercharging with water-soluble vitamins has no important benefit in normal man (112, 14, 59) but the situation with debilitated persons may be very different. Perhaps the conservative middle ground at present would be to suggest that convalescent patients receive supplements of the appropriate water-soluble vitamins if their daily urinary output contains less than 100 micrograms of thiamine, or 250 micrograms of riboflavin or 15 milligrams of ascorbic acid. These levels may be unnecessarily high. Far lower levels for months at a time are not associated with any deterioration in normal young men (60, 61).

The bodily stores of water-soluble vitamins appear to be smaller than the fat-soluble group. Definite signs of deficiency of thiamine may be induced in man in a few weeks or even days when the vitamin intake is zero, so the danger of a sudden onset of deficiency is correspondingly great. Fortunately, it is possible to correct such a deficiency rapidly by moderate doses of the vitamin. On a zero intake clear signs of deficiency of the rest of the B complex and of ascorbic acid do not normally appear for at least a month. The effect of concurrent disease is unknown.

On the basis of animal experiments and some

inadequate evidence from observations on man it is claimed that the human requirements for thiamine and ascorbic acid, and perhaps other water-soluble vitamins, are increased at high temperatures (83, 84, 50). The argument that these vitamins are lost in sweat has proved erroneous (82, 108). Brief supplementation with these vitamins has no effect on the primary course of adaptation to heat (48). There would appear to be no need to supply extra water-soluble vitamins for patients receiving heat therapy or convalescing in hot climates.

Thiamine. Several factors have been reported to increase the requirement for thiamine. Hyperthyroidism, both spontaneous and experimentally mentally induced, enhances the need for thiamine (32); whether this is caused by increased destruction is not known. In other conditions associated with an increased metabolic rate—hyperpituitarism and fever—there may be a similar need for extra thiamine but no evidence is available.

It is frequently stated that hard physical exertion increases the requirement for thiamine. This is based on the experiments of Cowgill and associates (27) who found that dogs on a B-deficient ration developed anorexia faster when they were exercised. Clinical reports on beri beri have indicated a greater incidence of the disease among men during hard physical work such as stokers and boilermakers. As yet, however, there is no bona-fide evidence in humans that the thiamine requirement is increased by work. Many people have argued that since thiamine is involved in the oxidation of pyruvic acid, there must be an increased need for the vitamin during exertion. However, blood pyruvate is not increased in moderate exertion.

The dietary intake of vitamin B_1 by animals can safely be reduced when the fat content is increased (105). There is some evidence that the same is also true of the protein content of the ration (7, 121). The evidence from human experiments is not so clear. Cahill (19) found no increased excretion of thiamine with a high fat diet for three days nor did he find any difference with test doses of thiamine following eleven days of high protein diets when compared with a high carbohydrate diet. He assumed that if the requirement for thiamine were decreased by the high fat diet, the urinary excretion should increase. A similar experiment gave variable results (124).

Gastro-intestinal disturbances affect thiamine absorption. A chronic diarrhea in the dog may increase the dietary requirement for vitamin B by 20 to 80 per cent (30). The diarrhea did not, however, "wash out" any of the vitamin given parenterally. Several clinical reports have indicated a marked therapeutic effect of thiamine when given to patients with mucous colitis and chronic diarrhea (20). There is a possibility that excessive amounts of thiamine may be lost in polyuria. Excessive water intake accelerates the appearance of symptoms of vitamin B deficiency in dogs (26). It has been assumed that in diabetes insipidus and in uncontrolled diabetes mellitus, the water-soluble vitamins are "washed out." No clinical work has been reported on this subject and experiments in this Laboratory have been negative. The diuretic substance, mercurophylline, may increase the excretion of thiamine in the urine (126). Other drugs may have a similar action; this question warrants further study.

Nervous symptoms associated with beri beri and experimental thiamine deficiency led to many sweeping conclusions about the possible role of this vitamin in nervous disorders in general. The earlier enthusiasm has been replaced by a more critical evaluation and a marked limitation of the conditions amenable to thiamine therapy (42, 76). The evidence that delirium tremens and other symptoms of chronic alcoholism are directly related to a specific thiamine deficiency is none too valid. The chronic inebriate secures most of his calories from alcohol and only a small fraction from food with a concomitant reduction in the intake of thiamine as well as other vitamins. In most cases thiamine has been combined with other therapeutic aids applied to these patients. There is fairly good evidence that many of the symptoms of Wernicke's disease are due to a restriction of the thiamine intake but here again treatment should consider the possibility of a multiple deficiency. Prolonged thiamine deficiency in animals is unaccompanied with any nerve degeneration (36). Recent work suggests that the metabolism of alcohol may require less thiamine than the metabolism of carbohydrates (69).

A chronic deficiency of thiamine both in experimental animals and in man produces cardiological disturbances. The congestion of the right side of the heart which is common in beri beri and alcoholics responds dramatically to the administration of thiamine. However, thiamine therapy for right heart failure is unwarranted unless there is a possible nutritional basis for the disturbance.

Theoretically many of the symptoms of diabetes would appear amenable to thiamine therapy but it now appears that thiamine only benefits the patient in relation to his dietary restriction (100). Where the diet has been deficient in vitamins because of restriction, natural supplements such as yeast or liver extract should be used since multiple deficiencies are probably involved. Large amounts of thiamine do not reduce the requirement for insulin (100).

The role of thiamine in preventing or overcoming infectious diseases is still unsettled. Under most circumstances vitamin B deficient animals

are less resistant to infection (93). A more important question is whether a "subclinical" deficiency will predispose the individual to disease. The prominent role that inanition plays was stressed by Rose and his coworkers (101, 102). They found that when the food intakes of the vitamin supplemented and the deficient animals were controlled, a deficiency of the B complex in rats produced very little change in resistance to *Staphylococcus aureus* or to *B. welchi* toxin.

Riboflavin. The estimation of the nutritional status of man with regard to riboflavin is even more controversial than with regard to thiamine. We believe the N.R.C. recommendations for riboflavin intake greatly overestimate the normal requirement for this vitamin (61). It is generally believed that riboflavin has an important role in muscular metabolism yet fatigue or weakness are not common symptoms of riboflavin deficiency.

Low urinary excretion of riboflavin has been considered the earliest diagnostic indicator of an incipient deficiency of this vitamin. Large doses of thyroxin increase the riboflavin excretion of rats (118) but the actual requirement for this vitamin does not seem to be affected (33). The injection of even moderate doses of thiamine into humans seems to increase temporarily the excretion of riboflavin (63).

Cheilosis and cheilitis are not specifically diagnostic of aribоflavinosis. Therapy with other vitamins, notably pyridoxine and niacin has produced satisfactory results (71). Many reports have not considered the fact that "cheilitis can result from sensitivity to dental plates, lipstick, chewing gum, toothpaste, mouthwashes, cigarette holders, throat lozenges, the reed used in the mouthpiece of a musical instrument, or to other agents, including even exposure to the sun" (90).

It has been suggested that exposure of the eyes to glare and bright light increases the need for riboflavin (94) (120) yet controlled experiments seem to be negative. The possibility of riboflavin deficiency must be considered in all cases of chronic nonspecific ocular complaints but such symptoms as ocular fatigue, mydriasis, photophobia and lacrimation are even less diagnostic than corneal vascularization.

There is a report that drugs such as atabrin increase the requirement of rats for riboflavin (47). Mice on a riboflavin deficient ration show increased susceptibilities to infection with pneumococcus Type I (129).

Niacin (nicotinic acid). The frequency of pellagra would suggest that niacin deficiency may often complicate convalescence in some regions. The normal requirement of man for niacin is still very uncertain and little is known about factors which may influence this requirement. This state of affairs is likely to persist until better methods are developed for evaluating the status of niacin nutrition. We cannot agree that the measurement of the F_2 fluorescence in the urine is very useful (81).

Some experiments with dogs indicate that the general type of the diet may influence niacin needs (44). The frequent association of malaria with pellagra (9) suggests this disease may affect the niacin requirement but the explanation may be a coincident geographical distribution of the two conditions. It is quite possible that the niacin requirement of man is increased as it is in dogs by sulfonamides, especially sulfapyridine (125).

The dramatic response of mental symptoms to niacin in pellagrins led to the use of this vitamin in many cases of mental disease, especially paranoia. It is possible that only niacin-deficient persons are benefited. The claims for niacin therapy for unexplained encephalopathy in alcoholics and in the aged (58) cannot yet be appraised.

Both tropical and non-tropical sprue are apparently benefited by niacin but complete recovery requires in addition liver extract parenterally (72). Further work is required to show whether the diarrhea alone causes an increased need for niacin or whether there is a more fundamental disturbance of metabolism.

Other members of the B complex. A deficiency of pyridoxin in experimental animals is associated with a microcytic, hypochromic anemia and fits of an epileptiform nature. The latter finding was partly responsible for the attempts to cure Parkinson's disease, pseudohypertrophic muscular dystrophies and other similar conditions (5). Early work indicated favorable responses to large amounts of pyridoxin but more recent reports are much less sanguine (42). The best evidence in man indicates that most cases of hypochromic anemia are not benefited by large amounts of good sources of the B complex (85).

Choline is necessary for the maintenance of normal liver and kidney function in animals maintained on purified rations. The requirement for choline is modified by such dietary factors as methionine, cystine, protein and possibly others. Although a choline deficiency has been associated most prominently with fatty livers, experimental work indicates that this compound is ineffective in curing fatty livers produced by such substances as phosphorous and chloroform (11). The favorable effect of choline in portal cirrhosis of the liver is reported (16) (103). It is too early to fully evaluate the importance of this type of therapy.

Ascorbic acid. Classical scurvy is associated with retarded wound healing, increased bleeding tendency and decreased resistance to disease—all of which are of importance in convalescence. However a linear relation between vitamin C intake

and these factors cannot be assumed to extend into the subclinical and "normal" levels. Moreover classical scurvy probably involves additional deficiencies besides ascorbic acid (28, 98, 40).

Little is known about the effect of diet on ascorbic acid requirements. Claims for an increased requirement at high temperatures and loss of ascorbic acid in sweat have not been substantiated (82, 48, 108).

Shortly after vitamin C was discovered, many attempts were made to show a relation between the blood components associated with resistance and the intake of vitamin C. This work showed that even in severe deficiency there was no change in the complement, bacteriolysins or their similar factors in the blood (93). Ecker and associates (34) stated that the complement level as determined by a more sensitive test was directly proportional to the plasma vitamin C level. All of the recent evidence indicates no relation between these two substances (114, 39).

The ability of extra vitamin C to increase overall resistance is being studied in England. During the war, the English receive in their diet an average of 25 mg. vitamin C per day. The addition of another 25 or 50 mg. of vitamin C to the diet in controlled experiments has shown little if any decrease in the number of days the subjects are absent from school or work because of illness (55). These and other experiments (25) show that if humans receive a moderately normal amount of ascorbic acid, no greater resistance against disease will accrue to them by consuming excessive amounts of vitamins. The surveys on the plasma vitamin C level during the year show that the lowest levels occur in April or May (74). If it is assumed that the plasma level is an approximate indicator of the body stores of vitamin C, then the period of greatest depletion occurs later in the year than the greatest incidence of upper respiratory infection (December and January).

Fever in infection apparently elevates the requirement for vitamin C as indicated by a rapid fall in the plasma level (128); the simple increase of body temperature has no influence on either the plasma level or the excretion (91, 133). On the basis of rough balance studies Falke (37) calculated his febrile patients needed an extra hundred mg. of ascorbic acid daily. Intakes in excess of this amount do not appear to hasten recovery from febrile disease (2, 39).

In very severe scurvy there is practically no wound healing. Mild vitamin C deficiency in guinea pigs just maintaining weight produces mechanically weak scars after operation (8) and disturbances in traumatized muscles (64). Clinical evidence indicates vitamin C is important but certainly is not the only factor in proper wound healing; body stores of protein must be considered (46). The depletion of vitamin C reserves associated with surgery is not yet satisfactorily explained. Hunt (54) suggests that all patients receive 1000 mg. of ascorbic acid daily for three days before operation and 100 mg. daily thereafter. Divided doses should be used and the sodium salt may be given intravenously if there is any possibility of poor absorption.

Many types of gastro-intestinal disturbances may interfere with the absorption of vitamin C. In diarrhea produced by magnesium sulfate the excretion of ascorbic acid in the feces may be markedly increased and the plasma level may fall (3). If this action of magnesium sulfate can be confirmed, it indicates that vitamin C is more readily "washed out" of the body than are the members of the B complex (30). Certain types of intestinal bacteria destroy vitamin C. Under certain circumstances this may make it necessary to give the vitamin intravenously (131). The Sippy diet and other bland diets used for gastro-intestinal disturbances are frequently composed of foods low in vitamin C. The addition of a vitamin concentrate is usually indicated in these cases.

Since changes in the gums are such a prominent feature of vitamin C deficiency, many attempts have been made to cure all types of gingivitis by means of vitamin therapy. However local treatment alone is usually sufficient to clear up the trouble (70, 75) and the diagnosis of ascorbic acid deficiency from gingivitis is unwarranted without other evidence.

There are some indications that certain drugs containing arsenic, antimony or gold may produce an excessive destruction of vitamin C in the body (38). The treatment of anemia with ferrous sulfate may also require the use of larger amounts of vitamin C (38). So far there have been no controlled experiments on the use of vitamin C as a detoxifying agent in the case of lead poisoning (52) or as a cure for allergy (51) or as an adjunct in the depigmentation of patients with Addison's disease (56).

Vitamin D. The requirement for vitamin D by adults is unknown both for normal maintenance and for fracture healing (6). It is likely that any good convalescence program will provide adequate amounts of this vitamin in most cases. The diagnosis of vitamin D deficiency in adults is difficult in the absence of tetany or definite signs of osteomalacia. Positive laboratory evidence at present demands the elaboration of calcium balance studies.

Osteoporosis may occur as a result of steatorrhea but the mechanism is uncertain (13). In any case large doses of vitamin D seem to be beneficial in nutritional as well as in war osteomalacia (49, 109). There is evidence that increased calcification

generally can be induced even in elderly people by high intakes of calcium and vitamin D (79).

Vitamin D in very large doses has been advocated for a wide range of chronic or intractable conditions from arthritis to psoriasis (92, 17). The controversial nature of reports does not warrant discussion here. Presumably the vitamin has pharmacological effects beyond its ordinary vitamin activity.

Vitamin K. The value of vitamin K is well established in many conditions of hypoprothrombinemia (18, 17, 29). It is unnecessary to discuss here the problem of the newborn or the rare possibility of simple dietary deficiency of the vitamin. Prothrombin deficiency in adults most frequently results from faulty intestinal absorption of vitamin K or from primary liver disease. Either or both of these conditions may be complicating factors in convalescence.

Hypoprothrombinemia and the resulting bleeding tendency are readily shown by measurement of the blood prothrombin level but the amenability to therapy is dependent on the cause of the condition. Prothrombin deficiency resulting from primary damage to the liver is ordinarily not responsive to vitamin K therapy. However, the boundary is not clear between refractory hepatic conditions and those which respond to therapy. For example, little is known on this question in residual liver damage after malaria and chemotherapy.

Vitamin K is less readily absorbed from the intestine than most other vitamins and deficiency may result from lack of bile in the intestine and from any severe diarrhea or steatorrhea (18). The latter conditions are important in ulcerative colitis and sprue and probably also in amebic and chronic bacillary dysentery. The increased frequency of these latter dysenteries incidental to war indicates the need for study of vitamin K and prothrombin relations in these conditions.

It is now common to attempt to correct vitamin K deficiency in surgical patients with biliary or hepatic disease or with extensive short-circuiting operations on the intestines. The possibility that unrecognized spontaneous bleeding or frank hemorrhage may occur to delay convalescence would make it desirable to consider these questions in convalescents who may have faulty absorption of vitamin K from any of the causes mentioned. Even though it is suspected that a demonstrated hypoprothrombinemia is due to primary liver disease vitamin K therapy should be tried. Failure of such therapy is in itself a useful diagnostic acid.

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EVALUATION OF FITNESS

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One of the goals of rehabilitation therapy is to return the patient to his work in good condition. Measures instituted during convalescence to more rapidly achieve this goal must be assessed by objective criteria. The physiologist and the psychologist can provide tools which will give some objective evidence of the returning fitness of the convalescent.

The term "fitness" is generally used to cover two distinct fields. One deals with estimation of occupational work capacity, the other has for its goal the assessment of the ability to withstand physical and biological stresses. These fields overlap and are frequently confused. Tests of cardiovascular, respiratory and metabolic processes, motor performance, sensory and intellective functions, and emotional state will be reviewed to give a rounded picture of fitness of a general character which is not closely related to a specific occupation. Particular emphasis has been laid on the limitations of these procedures and on valid experimental design.

All fitness tests are extremely non-specific and should always be interpreted in the light of clinical findings. No attempt has been made to review the problem with reference to particular disease entities; cardiovascular and respiratory tests have been evaluated from the clinical point of view by Simonson and Enzer (1).

The problem of standardization. The great majority of fitness tests, whether physiological or psychological, appear to be extremely simple. However, the functions measured are subject to a great variety of influences and it is necessary to apply the most rigid control of environmental, physiological and psychological conditions under which a measurement is carried out. It cannot be stressed too highly that pre-test exercise, time relation to meals, psychological "atmosphere," and environmental temperature and humidity must be kept as constant as possible.

Psychological factors are of importance in many fitness tests. All psychomotor and maximal exertion tests (2, 3) have as a prerequisite the optimal motivation of the subject. Control of emotional factors is imperative in pulse rate tests—such as postural adjustment (4), the Schneider test (8-A) and the Masters' test (5)—in which the stress placed on circulation is low.

In laboratory work an attempt is usually made to bring the individual subjects to a practice plateau before they are exposed to the experimental regime. Under these conditions we can work with a smaller number of subjects, each serving as his own control. Under clinical conditions we do not have a "normal baseline" characterizing the patient in the state of health; the degree of returning fitness must be judged by reference to adequate norms. These may be developed either 1) for the general population (taking into account the improvement on repeated measurement due to the specific effects of practice) or 2) for a relatively homogeneous sample of patients.

The importance of controlling environmental temperature and humidity for any test which in-

volves the measurement of cardiovascular variables has not been duly recognized until recently (6). For example, several serious attempts have been made to set up norms for tests depending in a large measure on pulse rate and blood pressure measurements (5, 7, 8, 9). In no case has an adequate correction for temperature or humidity been included. The evidence is overwhelming that differences in temperature influence these scores (10, 11, 12). The use of air conditioned testing rooms has eliminated this difficulty in the Laboratory of Physiological Hygiene.

Cardiovascular and respiratory tests. The cardiovascular and respiratory systems are usually tested under stress. Basal pulse rate and blood pressure measurements are of value only when the emotional situation is properly controlled, i.e., when the patient is accustomed to his surroundings and the observer, and does not attach importance to the measurement or to subsequent events (13). The two types of stresses most frequently employed are change of posture and performance of physical work.

For general testing where specific occupational requirements are not being considered, the work should require as little skill and coordinated use of local muscle groups as possible. Of the four tasks most commonly used, riding the bicycle ergometer is probably the least satisfactory due to large skill increments. Both stair and step climbing, although involving some degree of skill, are well adapted to work in the field or clinic where more elaborate methods are not applicable. For repeated observations over a period of time, grade walking or running on the motor-driven treadmill appears to be the most desirable work load since 1) skill is rapidly acquired, 2) the true work efficiency remains remarkably constant after subjects have learned the "trick," and 3) the work output for each subject is constant.

The heart rate after a standard amount of work is probably the most useful single criterion of fitness in the study of convalescence. It has been shown that the pulse rate recovery curve can be satisfactorily reconstructed from three measurements (2). In developing a test which might have some general use in convalescence the investigator is faced with a dilemma. While it is desirable to use heavy work loads to obtain a good differentiation of degrees of fitness and to eliminate or minimize emotional effects, heavy work loads may injure the patient and delay recovery. The use of post-exercise pulse rates of 130 to 150 per minute (during the first 15 seconds of recovery) will do much to eliminate emotional factors and at the same time give a satisfactory estimate of cardiovascular fitness without too much danger of injuring the patient. The establishment of minimum work pulse rate values which are not influenced by emotional effects (such as are present in a medical examination) is one of the critical problems in the field of cardiovascular fitness.

For postural adjustment studies the tilt table will provide the most reproducible stress. Postural adjustment tests either with or without a tilt table might be expected to give some useful information since evidence of poor circulatory response to postural changes is common in the early stages of convalescence. Poor postural adjustment has been found to be associated with certain diseases (14) and as the result of surgery on the autonomic nervous system (15). In the morning the postural adjustment score may show progressive deterioration, while it may indicate progressive improvement in the afternoon (11, 15). Response to postural adjustment is not closely related to ability to perform exhausting work (13). Caution should always be exercised in interpreting the results of these tests.

In any battery of tests for use in clinics the Flack test (17) or one of its modifications should not be ignored. It has been shown to differentiate well between active men and convalescent patients (9, 17), and significant improvements have been recorded after a period of physical training. The high dependence of this test on the willingness of the subject to exert himself may yield useful information.

Hard work tests should give information on the status of the patient on discharge or on the progress of a training program to put men in top physical condition. In precise laboratory investigations fitness estimates may be obtained either by using a fixed run on a motor-driven treadmill which represents work near the limit of a subject's capacity or by allowing the subject to run to exhaustion within 3 to 5 minutes. Measurement of the maximal pulse rate, maximal oxygen consumption and respiratory efficiency during work, and determination of pulse rate, blood lactate and respiratory efficiency during recovery will provide the basic criteria. The pulse rate during recovery from a fixed task is an index of fitness while if the subject is allowed to run to exhaustion the recovery pulse will not reflect changes in the subject's condition (18). After a fixed work period, the lower the lactate (taken at a constant time after work) the better the condition of the subject; the reverse is true if the subject continues to run to exhaustion (19). The measurement of maximal oxygen consumption is, on theoretical grounds (20, 21), the best available test of the over-all function of the combined respiratory-cardiovascular system. It is a relatively constant characteristic of a subject and when changes are observed they indicate a more fundamental deterioration or improvement than changes in such variables as the pulse rate. The respiratory

efficiency either during work or recovery serves as a standardized index of ventilation and is related to the degree of "exhaustion" (22, 23) of the subject, but has the disadvantage that artefacts due to improper masks, etc., occur easily. The measurements of the maximal pulse and oxygen transport during an exhausting work test are independent of the skill of the subject. Blood lactate measured under the same conditions is dependent on motivation but independent of skill.

The use of a fixed task has the advantage that all the measurements are independent of motivation. The recovery pulse rate is a more sensitive index of fitness than the maximal pulse rate during work and does not require elaborate methods for measurement. Proper choice of length of time for the standard work is necessary for measurement of maximal pulse and oxygen consumption. The use of this method is open to two objections: 1) the measurements reflect any increase in skill in running that subjects may acquire by repeated testing, and 2) a number of different work loads must be used to cover a wide range of physical capacities.

The adoption of uniform procedures chosen on a rational basis would be a real advance and would allow the establishment of norms and interlaboratory comparison of data.

Many investigators have used the measurement of the working time to exhaustion as the principal criterion of fitness (2, 3, 6). This fitness estimate has been combined with pulse rate measurements during recovery (2). The use of a double work period has served to reduce the intra-individual variability on successive measurements (3). When the subject cooperates, these tests give valid information and correlate well with other measurements of fitness for physical exertion. For example, studies in this Laboratory have shown that the score in the treadmill version of the Fatigue Laboratory Test (2) gives high correlations with blood lactates and pulse rates during recovery from a fixed anerobic work test. In situations where the effectiveness of a given regimen is to be studied, this type of test gives valid information if the following conditions are fulfilled; (1) the use of sufficient numbers of subjects to rule out uncontrolled variations in motivation, and (2) the use of inter-group controls to rule out errors inherent in group behavior (suggestion and imitation). These methods are ideally adapted for use with large number of subjects. Repeated testing will lead to sizeable improvements in score due to increase in skill, a fact which demands inclusion of controls. In military convalescence these tests should prove of real value in determining whether or not a man is fit to return to duty. Suitable standards of post-exercise pulse rates can be set up to screen out men who do not co-operate.

Metabolic measurements of fitness. No constituent of the resting blood is closely correlated with fitness for muscular exertion. The utility of lactate measurements during or after work for assessing fitness for muscular exertion has been discussed. Advances in this aspect of fitness may come from study of the newer compounds of the Meyerhof cycle together with blood lactate and pyruvate.

The vitamin concentrations in blood or urine are regularly used for nutritional assessment (25) but it is too early to make any statements on the precise relationship of these constituents to fitness. Work in this Laboratory suggests that these relationships are not very direct.

Metabolic load tests give useful information in some situations. The study of pyruvate concentrations during a glucose tolerance test will give evidence of thiamine deficiency (25).

It is well recognized that adrenal cortex responds to stress placed on the organism and it is also well known that adrenalectomized animals are less resistant to a great variety of biological stresses (26). The fact that 17-keto steroids reflect adrenal cortical activity (27) suggests the possibility that the concentration of these compounds in the urine will reflect the stress placed on the organism and may be used as a criterion of fitness. It has been shown that a high positive correlation exists between 17-keto steroid excretion and fatigue states in flyers (28). Previous experimental work (29) has indicated that little advantage in work performance can be obtained by administering hormones of the adrenal cortex to men in good condition. The possibility that these hormones may be an aid in more rapidly attaining a state of physical training should be investigated.

Motor performance. The fundamental aspects of voluntary motor behavior can be classified as (1) maintenance of static position (body sway), (2) gross body movement (locomotion), and (3) manipulative components (strength, speed, coordination of movements carried out by specific muscle groups). When the performance is of short duration and the tests are carried out with the subject fresh and well motivated the score represents a true performance capacity. The difference in performance observed under stress and normal conditions may be used as a measure of endurance (fatigability).

Strength is measured as the maximum force that can be exerted; the score can be evaluated with reference to general population norms. Under certain conditions, e.g., in poliomyelitis where only some muscle groups are affected, it may be more meaningful to determine the strength of a particular group of muscles in relation to the strength of other muscles. Speed can be determined either as the average time needed for a movement or as the rapidity of successive move-

ments, e.g., in tapping. Accuracy refers to the spatial characteristics of a movement and can be measured, e.g., as a deviation of the hits from the center of a target. In occupational work, accuracy usually involves not only a purely spatial character but also the element of timing and of gradation in strength. The extent of movement is of special interest in pathological conditions where one can determine either the arc through which a part of the body can be moved at a joint or the accuracy with which a movement can be voluntarily reproduced.

Systems of athletic tests which score a performance simply as "success" or "failure," such as the Brace scale of motor ability tests, may be useful for the establishment of gross differences between individuals and can be given as a group test, thus saving much time (30). The Illinois motor fitness screen test (31) is also based on an "all-or-none" principle of scoring of each of the 14 items. In research work in which the improvement or the deterioration of individuals is studied, one should select performance which is capable of fine gradation and of objective evaluation. These tests are usually of the analytical type and attempt to measure single aspects of motor performance such as speed or coordination in a "pure" form. The more simple a performance, the easier it is to standardize the work method; also, the amount of training necessary to reach a plateau is proportionately smaller. On the other hand, it appears that the simpler responses are less sensitive to stress.

Our experience confirms the statement that "for both receptive processes and active processes the evidence of deficit becomes more pronounced as performance becomes more complex" (32A). We have found that in the face of stress—such as starvation—simple strength is affected least; the complex performance of pattern tracing shows the largest deterioration; tapping and gross body-reaction time are intermediate.

Where one deals with the rehabilitation of patients who will be returned to a specific job, the use of complex "miniature job situations" to test the performance level has its advantages. The importance of standard job tests for selective purposes was emphasized by Drake (33). Goldstein (34), in his study of brain injuries, included both "abstract" performance tests (simple and choice reaction time and ergographic tests) and the "concrete" tests (workshop method). It is becoming apparent that job performance is more than a sum of its sensory and motor "elements"; direct study of complex activities having important "mental" components reveals behavior characteristics which cannot be derived from the separate study of "local" neuromuscular mechanisms. This is well illustrated in Bartlett's study of the deterioration in pilot performance resulting from work fatigue; the isolated local actions of control could still be carried out satisfactorily while the organized, coordinated and timed responses could not be maintained (35). An example of a partly specialized battery is found in the Psychomotor classification tests of the Army Air Forces (36).

Changes in motor performance in disease or in convalescence have not been studied extensively although weakness and exaggerated body sway, incoordination and sluggishness are frequent clinical symptoms, capable of quantitative evaluation. When the standardized test techniques have been applied to these situations they have been shown to be useful as criteria of fitness.

Co Tui et al. have been able to measure improvement in strength and endurance in convalescent surgical patients by the use of a new bedside ergograph (37). Brahme described a similar instrument (38) which will measure the ability to maintain a maximal grip or record successive performance following each other in a given tempo. Curves of patients recovering from various diseases illustrate the results obtained with this technique. Whereas a group of patients who received treatment for chronic polyarthritis averaged on admission 27.4 kgm./min. (minim. 11—max. 67), on discharge they had an average score of 67.4 kgm./min. (minim. 34—max. 94). Ergographic records, together with tests for electrical excitability and electromyograms recording the electrical action potentials released during muscle contraction, have been used successfully for quantitative measurement of regeneration of injured peripheral nerves (39). The authors report that this method yielded significant information in cases of poliomyelitis and infectious polyneuritis.

The findings on deterioration of motor processes in psychiatric patients have been summarized by Hunt and Cofer (32B). In a number of psychiatric groups the average reaction time was longer than in normal individuals; also, the intra-individual variability increased.

Tapping, regarded as a measure of the efficiency of motor centers, was investigated in patient with circulatory insufficiency (40). The maximum frequency of motor responses per unit of time was reduced and fatigability increased. Finger ergographs, muscle strength in "back pull," heavy dynamic and static work (lifting and horizontal holding of dumbbells), together with circulatory and respiratory tests have been used to demonstrate that methyltestosterone treatment of patients with diminished production of sexual hormone increased muscular performance (41).

There is an increasing use of quantitative performance tests in the study of the recovery from direct neuromuscular impairment or muscular

deterioration resulting from fractures. As an example of the first category we may mention the work of Molander and Weinmann (42) on poliomyelitis, in which various objective tests were given through a period up to 3 years to follow improvement in muscle function. The examinations included (1) functional classification of muscles, based on the ability to perform a simple movement against gravity and resistance; (2) determination of the active and passive range of motion on a protractor scale; (3) muscle strength, measured by a set of spring balances; (4) endurance expressed as a rate of decline on the muscle strength tests repeated in succession 10 to 15 times.

It may be expected that significant improvement in the methods for evaluation of motor fitness will come out of the intensive rehabilitation program which is being developed by the armed forces. For example, at the Fitzsimmons Hospital (Denver) observations are made of the physical performance of convalescents during their activity program. In addition, repeated measurements of physical and motor fitness are made and postural examinations are also carried out in order to obtain a comprehensive and meaningful picture of the progress of convalescence (43). Unfortunately the full details are not yet available.

Experiments on the effects of enforced bed rest on normal men are in progress at this Laboratory. One aspect of this program is the study of motor deterioration and recovery. The preliminary results suggest that the ataxiameter, measuring the amount of body sway, shows the largest deviation from the control values obtained before the subject was put to bed; repeated measurements show improvement reflecting the course of recovery. Pattern tracing, a complex motor task performed while the subject walks on the treadmill and requiring a good deal of eye-hand coordination, and the test of strength of the trunk muscles ("back-pull") showed also a significant deterioration when measured in post bed-rest conditions. The strength of grip (hand dynamometer) and the speed of movement as measured by ball-pipe test and tapping did not change appreciably.

Sensory and intellective functions. On theoretical grounds we may expect that in disease the central nervous system will be resistant to deterioration. Actual knowledge of the effects of pathological processes on sensory and intellective functions is limited.

The effects of some of the basic physiological factors (oxygen supply, blood sugar level, acid-base balance of blood, nutritional and endocrine factors) have been reviewed (44). In discussing the effects of disease, Shock stated: "While hereditary syphilis may interfere with mental development in young children if left untreated, there is no good evidence that diabetes, tuberculosis, heart disease, or allergy causes significant alterations in behavior because of their physiological effects. On the other hand any disease may have profound effects on behavior by influencing the social environment of the patient" (44).

In poliomyelitis resulting in motor deterioration, the intellective functions seem not to be impaired (45). There is some evidence that learning ability in children is impaired when they are maintained on a low thiamine intake (46).

The disturbance of perception is of importance in various mental diseases and in cerebral injuries (34). It has been found that manic depressive patients exhibited a slowing down of the rate of fluctuation in ambiguous figures (47). We found a slight decrease in subjects severely restricted in vitamin B complex intake. Critical fusion frequency of flicker (F.F.F.) as an index of the efficiency of the sensory centers was studied under conditions of general fatigue, drug stimulation and in disease. This measurement might be used to study recovery in post-concussion states (48). F.F.F. was reported as decreased in circulatory insufficiency and in patients with hypothyroidism (49). Improvement of visual functions and in psychomotor performance has been demonstrated following the use of cold hip baths (50). In this Laboratory we have investigated changes in the peripheral visual field in normal young men subsisting on inadequate food and water intakes. A progressive decrease in the size of the visual field was observed, from 5 per cent on the second day to 11 per cent on the fourth day along with a 7.3 per cent loss of body weight. Gellhorn and Hailman have made a survey of visual and other sensory measurements which are useful in the study of the effects of anoxia (51). In studying pain heat, electrical current and mechanical pressure can serve as calibrated stimuli. Attention may be paid either to the liminal values (pain sensitivity) or to the maximal stimuli tolerated (pain tolerance). Pain sensitivity is more directly related to the immediate neuro-sensory mechanisms; pain tolerance may be expected to involve to a greater extent the personality factors and serve as a broader index of the capacity for tolerance of discomfort having appreciable correlation with willingness to exert physically.

Emotional status. In research on "physical fitness" the study of emotional status related to "morale" is of acknowledged importance. For the most part we have to deal with the feelings of well-being rather than with personality (character, temperament, attitudes, interests), although the latter provides a frame of reference in which the changes in emotional adjustment will be expressed and, occasionally, may become an integral part of fitness research. Changes in personality have been

studied in the Laboratory during partial and acute restriction of vitamin B complex intake. Subjective questionnaires, inter-individual ratings, Cattell's Cursive Miniature Situation (C.M.S.) Personality Test (52), Minnesota Multiphasic Personality Inventory (54) and the Rorschach test (54) were found to be useful.

Subjective questionnaires can be designed to indicate the presence or absence of "neurasthenia symptoms" or they may be directed to more specific subjective difficulties arising in a particular stress situation. Data from a study of the effects of subsistence on a very low level of caloric and water intake illustrate the latter condition. Besides the general symptoms of discomfort (headache, dizziness, feeling of being "shaky," tiredness, irritability, decline of mental alertness, etc.), the questionnaire included more specific items such as nausea, dry mouth, gastrointestinal distress and hunger. The response categories were "absent or normal" (weight 0), "more than normal" (weight 1), "quite a bit" (weight 2), "very much so" (weight 3). A general trend of deterioration can be expressed by an over-all score which corresponds to the weighted sum of the 20 items. The average P.M. scores on the successive days were 5.4, 10.2, 13.7, and 16.2.

We are well aware of some of the difficulties involved in subjective questionnaires. Judgments, especially as to degree, depend upon strictly personal criteria, upon introspective ability which varies from individual to individual, and the memory of previous states of feeling. In long-term experiments or in convalescence the changes may be very gradual and therefore easily missed. However, we may expect that there will be considerable differences between different traits rated. Thus a subject or a patient will be less able to estimate his "mental alertness" than a headache or presence of thirst. The final criterion of the value of this technique is operational. Does the questionnaire, under well controlled conditions, show differences where there are differences in the experimental regime?

Comments. Schneider (8B) states that "physical fitness" is frequently taken to mean general health. This is an unfortunate confusion of terms since a high degree of athletic performance is compatible with some disease states (55). Furthermore, the assumption (commonly used in validating tests which might be useful in differentiating degrees of health) that a group of athletes is "healthier" than a group of sedentary workers, both groups being certified by a physician as free from disease, does not appear to be based on valid evidence. It is most unlikely that an individual who is fit to resist one stress (physical exertion) will be fit to resist all stresses. For a more precise definition of the relationships between fitness tests and health, two questions might be considered: the sensitivity of these tests to deterioration and their ability to predict resistance to stress.

Tests of the general type discussed above have been used successfully in many stress situations; as examples one might mention that cardiovascular and respiratory tests are sensitive to many acute and chronic diseases, to the stress of heat, anoxia and exhausting exercise, and that sensory and psychomotor tests are sensitive to anoxia, loss of sleep, old age, and starvation. It is apparent that the degree of systemic deterioration can best be determined by the combined use of physiological and psychological methods. However, much remains to be done in developing more sensitive tests in specific situations. For example, there is no test sufficiently sensitive to the stress of ordinary industrial work.

The limitations and advantages of fitness tests will be more clearly defined when we know what combination of fitness tests, new or old, will predict ability to withstand the following stresses: starvation, anoxia, heat, cold, toxic agents, noise, loss of sleep, common infections (such as colds, flu, etc.), malnutrition and development of degenerative diseases such as hypertension and arteriosclerosis. At first glance such a program appears to be overly ambitious and technically impossible. However, two attempts in this general direction give hope that this goal can be reached: successful prediction (24) of the ability to acclimatize to high altitude, and the progress that has been made in the use of the cold pressor test in predicting the development of hypertension (56).

Vocational guidance based on objective assessment of physiological and psychological aspects of work capacity, vocational retraining and selective placement in industry (or in the armed services) are important parts of rehabilitation programs (57). In vocational guidance and selection special standardized tests which have been validated against specific criteria of job success must be used (58, 59). Further research on the relation between physical and mental make-up and efficiency in industrial work is needed. Particularly the *minimal* fitness standards compatible with efficiency of production and safety on the job will require increased attention.

Simonson (60) estimates that in about 80 per cent of all jobs in industry muscular effort is slight or moderate. Under these conditions the study of sensory efficiency, especially in the visual area (61), and of motor performance assumes proportionately greater importance than the biochemical and cardiovascular changes. However, the degree of cardiovascular fitness compatible with efficient work in different types of industrial

occupations constitutes a problem of obvious importance in convalescence studies.

In much laboratory fitness testing an attempt is made to probe into functions which represent biologically meaningful components of work capacity. It is in *this* sense that one may speak of general fitness, *not* that any single test measures a hypothetical "common factor" involved to the same degree in all kinds of motor, mechanical or exhaustive performance. This Laboratory has made an effort to develop a battery of general tests which samples the basic components of a wide range of activities and provides a basis for broader inferences as to the effects of an experimental regimen on fitness.

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CARDIAC ASPECTS OF CONVALESCENCE

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The rôle of the heart in convalescence may seem at first glance to be a minor one. However, even in conditions which do not involve primary defects in the heart muscle, the coronary flow, the heart valves or in the excitation and conduction system, there are obviously three general types of situations in which cardiac physiology is crucial to the problem at hand. First, it is apparent that the onset of cardiac failure is the critical occurrence which ultimately determines life or death in numerous situations. Second, the cardiac reserve capacity is undoubtedly one factor determining fitness for physical exertion following illness of various sorts. Third, the activity of the heart in the integrated circulatory system is a central problem in neuro-circulatory asthenia or Da Costa's effort syndrome, and in related states. The problem of convalescence in the specific disorders of the heart itself will not be considered at this time.

A critical review of existing information on the rôle of the heart in the physiology of convalescence is an extremely difficult and unsatisfying assignment because a comprehensive coverage of the tangentially applicable literature would require an amount of time and space probably unwarranted by the value of the result, and because there are so few observations bearing squarely upon the problem. It has seemed to the author, therefore, that a better purpose would be served by outlining the problem broadly, bringing into the discussion the relevant facts with which he is familiar and suggesting possibly fruitful lines for further study.

A review of Biological Abstracts and the Quarterly Cumulative Index Medicus reveals very few entries which bear directly upon the problem of the heart in convalescence in the absence of frank heart disease. These few deal with such subjects as cardiac abnormalities in avitaminosis, in endocrine disorders, in such infectious diseases as diphtheria and comparable topics. The physiologist is treading on dangerous ground and must be cautious when he discusses the functional significance and problems of an organ in convalescence generally, disorders of which are ordinarily believed not to be critical to survival or full recovery. It is a principle of first importance that in considering any scientific question the relative importance of the various factors involved be established. The astute physician cannot be concerned too much with minor matters when major issues are at stake. After the more important factors have been dealt with is the time to pay attention to the less critical ones. Therefore, his lack of interest in the heart in convalescence may indicate that the physician has reason to believe that the heart is of less importance to survival and full recovery than are other organs. On the other hand, it may be that some important factors are being ignored.

It is an interesting and arresting fact that with progress in medical knowledge the exhibition of drugs purporting to "support the heart" in non-cardiac disease has progressively diminished. In the main, drugs other than the cardiac glycosides employed in the past and even at the present time, supposedly to strengthen cardiac contraction, actually operate upon the peripheral vascular system. To be sure such action has a round about effect upon the condition and the work of the heart by altering the venous return and the coronary circulation, but the primary action is upon the peripheral blood vessels and not upon the heart. An example is coramine, which has no direct cardiotonic action (1), but may nevertheless be a useful drug. Even in the cases of agents such as the sympathomimetic amines, natural and synthetic, which do act directly upon the myocardium as well as on vessels, their main effect in the usual doses is probably exerted via their vascular actions.

1. *The principles of cardiac physiology bearing upon the convalescence problem.* As a part of the total organism the whole function of the heart is to deliver blood in a continuous manner to the other body organs in amounts adequate to their needs for survival and activity. In order to perform this service to other organs the heart must be capable of converting certain amounts of chemical energy into mechanical work with at the least a certain minimal efficiency. Again, for this to occur the myocardium must be supplied with at least its minimum metabolic needs for energy and repair, and must be rid of metabolic wastes. Thus for its continuous operation the heart is dependent upon the proper functioning of such organs as the lungs, the liver and the kidneys.

On the hydrodynamic side the ability of the heart to function effectively as a pump depends upon the state of the vascular system. In common with every other machine doing work the heart does its work with varying efficiency depending upon the conditions of loading. In general the efficiency of the heart falls off as its filling decreases. Therefore when the venous return diminishes the heart becomes inefficient as a machine.

This is perhaps the most important physiological phenomenon in connection with peripheral circulatory failure. In any situation in which there is a sufficient primary decrease in venous return, be it due to diminished blood volume or to peripheral blood pooling, the heart itself becomes progressively less able to deliver adequate stroke volumes under sufficient pressure to maintain the coronary and peripheral vascular flows, and unless the vicious circle is broken the process leads irrevocably to to death. So it appears that in the last analysis it is progressive cardiac failure that forms half of the circle in the round of events which causes the fatal outcome in states with reduced blood volume, as in shock or hemorrhage, and in states of peripheral vascular collapse (dilation), such as terminal toxic infectious states, histamine poisoning and other anaphylactoid and perhaps anaphylactic reactions, heat stroke and other disorders.

On the metabolic score the heart fails as its fuel supply is exhausted and as certain, as yet unknown, metabolites increase. In the isolated heart, failure occurs with fuel supply (glycogen) adequate (2). Such failure ordinarily occurs without a decrease in total energy expenditure at a given diastolic fiber length, so long as the coronary flow remains high (3). Thus it is an efficiency and not an energy failure.[1] The chemical reason for such efficiency failure is unknown. The problem of ascertaining this chemical mechanism is a central one in the physiology of heart failure. A few clues exist. Experience with the use of the heart-lung preparation as the pump for perfusion of the kidney provides an impression that spontaneous failure of the heart is much delayed in such a system as compared with the heart-lung preparation alone. No critical experiments appear to have been carried out to test this question or the related ones as to whether other individual organs such as the liver may add to or remove from the blood substances influencing the failure process in the heart.

A great variety of substances and conditions have been tested for their failure-influencing effects. Increased work load, especially against high pressures, accelerates the failure process (4). So does increased acidity, relative oxygen want, elevated temperature and elevated right heart pressure which latter impedes coronary sinus and thebesian vein outflow, thus diminishing coronary circulation. The after effect of large doses of adrenaline is also one of hastening failure (5).

Since the degree of cardiac failure can be the critical factor determining survival or death in a variety of situations it seems apparent that an improvement in recovery rates might follow if better methods were available for reversing the trend toward progressive heart failure. Some rational measures are available, such as increasing the oxygen supply by administering higher tensions in the inspired air. Raising the blood volume is useful so long as the increased filling of the heart does not produce dilation with increased energy liberation, and thus precipitate final failure. The cardiac glycosides may have a useful application in certain instances.

However, the actual chemical factors underlying heart failure are still unknown. It is entirely possible that their elucidation will point the way to much more effective methods of supporting a failing myocardium free of structural defects. An obviously desirable line of study is in the more intimate chemical aspects of heart failure.

2. *Bed rest and cardiac reserve.* Prolonged bed rest is an element in so many treatment procedures that it deserves special consideration from several viewpoints. The work load upon the heart ordinarily depends so largely upon the amount of bodily muscular activity that bed rest reduces cardiac work toward the minimum compatible with life. Such a reduction may in certain stages of heart failure so lighten the heart's load as to initiate a reversal of the failure process. Presumably this comes about by decreasing the energy expenditure and therefore the oxygen consumption rate in the heart, allowing more complete approach to recovery and decreasing the concentration of activity metabolites, some of which latter are usually assumed to be responsible for the inefficiency of work performance that one sees in experimental failure. An alternative possibility is that the overworked heart exhausts itself of certain essential materials (not necessarily those supplying energy) whose replacement rate cannot keep pace with the loss rate unless cardiac metabolism requirements are reduced. In any case, reduction of cardiac work by bodily rest does bring about reversal in heart failure in man with great regularity in milder degrees of decompensation, just as a similar reduction in cardiac work sets up a reversal in the progression toward fatal inefficiency and increase in diastolic volume at constant stroke volume in the isolated dog or cat heart. The fact that such a reduction in cardiac work and energy expenditure reverses the trend toward progressive failure is adequate justification for achieving it whenever myocardial failure

[1] Two groups of investigators (6, 7) have reported experimental failure in the isolated and heart-lung heart to occur without efficiency decline. These observations have been reviewed previously (8). Other workers (9, 10, 11, 12, 13) agree that the efficiency declines in experimental failure except when coronary flow is interfered with.

is present. Thus absolute bed rest is indicated whenever cardiac insufficiency is present.

But reducing cardiac work has other effects, especially in the normal heart. So far as is known all muscular structures respond to increased loads of work, within physiological limits and under normal chemical conditions, by an increase in capacity to do work, and by increase in active mass. Conversely long continued relief from heavy loads is soon followed by an involution, functional and structural. The chemical composition of heart muscle may be considerably altered by heavy work. Swimming rats for example show elevated cardiac glycogen, particularly in the post-exercise period (14).

It is apparently an unsolved question what part of the debility of patients subjected to prolonged bed rest may be due to a primary cardiac weakness resulting from what might properly be termed partial disuse involution. It is not likely that such a cause would operate alone in most instances to bring about the low exercise tolerance, tachycardia on exertion and related symptoms in convalescents, but as a contributing factor of importance it cannot be ruled out without further study. Thus the effect of prolonged inactivity on cardiac reserve capacity, and the further consequences of the latter on fitness deserve greater attention.

3. *The assessment of fitness.* It is not accidental that nearly every so-called fitness test in current use (for references see (15)), utilizes, among other criteria, the changes in heart rate in exercise. There is a significant inverse correlation between heart rate at definite intervals after standard work loads over short periods of time and capacity to perform over longer periods. An oversimplification of the problem would be unfortunate but it can scarcely be doubted that, among other factors partly responsible for this relationship, the maximum (or perhaps optimum) stroke volume of the heart is a determinant (16, 17). A satisfactory analysis of this relationship has not been made. In spite of literally hundreds of fitness studies the underlying physiology has received scanty attention. Most workers have contented themselves with statistical evaluations of the practical usefulness of particular types of tests. Such studies have an important place and have resulted in definite improvements in evaluation procedures. Nevertheless there are still important discrepancies between prediction from fitness tests and performance (18) and it would seem unlikely that such discrepancies could be resolved without further fundamental study.

The cardiac acceleration in exercise is brought about mainly by nervous mechanisms. There is apparently a central nervous factor that comes into action at the onset of movement (19). Later reflexes control the heart rate to a large extent. The afferent arms of the reflexes brought into play are the nerves from the vasosensitive zones and proprioceptive nerves from the muscles, tendons and joints brought into action in exercise. The relative contribution made by each is unknown, and therefore the question of the limiting effect of cardiac work capacity on exercise heart rates is unsolved. A very important measurement which would assist in solving this problem would be that of right atrial (venous) pressure in exercise, in relation to heart rate changes. It is known that the venous pressure rises in exercise (20), and that the rise is roughly proportional to the severity of work (21) but that the increased heart rate minimizes the venous pressure rise. Apparently correlations of extent of rise with heart rate changes and with fitness have not been made.

In recent years the emphasis in fitness studies has been placed on the peripheral vascular system, the nervous system, particularly the autonomic division and upon skeletal muscle training. Without discounting the importance of those factors it seems obvious that the heart itself should not be neglected in these studies. The three most accessible important variables for measurement are the venous pressure, the diastolic volume and the stroke output. Together these quantities can be made to yield important information concerning the work capacity and efficiency of the heart and deserve much greater attention than they have received in fitness studies.

4. *The relation between heart rate and cardiac efficiency.* Since every fitness test indicates that high post-exercise heart rates are associated with poor performance (18), and since trained athletes tend to show low basal heart rates (16), it is of some interest to correlate these facts with more basic information. The isolated heart performs a standard amount of work per unit of time more economically as to energy cost the larger the stroke volume. In other words, for constant minute volumes the efficiency of doing work increases as the heart rate falls (22). This is due to the fact that over a wide range the loading efficiency increases with increasing volume loads (13).

Thus the lower the heart rate at which a given load can be carried the more efficiently can it be done from an energetic viewpoint. So it appears that the slower hearts are the more efficient ones and it is therefore not surprising that they can carry the heavier loads over longer periods of time.

To complete the picture of the influence of heart rate on cardiac energy expenditure the energy cost per beat must be considered. In this regard it has been found that at a given constant diastolic fiber length the energy cost per contraction decreases as the heart rate increases (22). The de-

crease in total energy cost is not nearly as great as the decrease in work output and therefore, as noted above, the efficiency falls. Nevertheless it is important to note that a tachycardia in a subject at rest need not increase cardiac metabolism in full proportion to the increase in heart rate. It is mainly when the work load on such a heart increases above resting levels that embarrassment appears. This fact permits the heart in the resting subject to beat at very high rates without the onset of failure, even in heart disease in cases where increased stroke volumes quickly precipitate decompensation.

To carry heavy loads of work the heart must have a high resting stroke volume and must be able to increase the stroke volume greatly in exercise. Without doubt, at least two factors enter into the latter. First, there is a tendency toward increased diastolic filling and increased energy output following the diastolic volume law. But the residual blood decreases too, as is evidenced by the smaller systolic volume (23), and since the mean systolic blood pressure is not reduced in exercise one is forced to conclude that a second mechanism comes into play, namely a change in work capacity at a given diastolic volume. This change is comparable to the one produced by adrenaline in the isolated heart (11). It is not an unreasonable supposition that adrenaline (sympathin) is mainly responsible for the effect in the intact organism.

Since the rate increase is only one of the effects of adrenaline upon the heart it would seem that the subjects with the faster resting heart rates might be continuously under the influence of abnormally high levels of adrenaline in the heart muscle. This effect might be, and probably is, disadvantageous to the mycocardium. Very small amounts of adrenaline plus cholinergic drugs increase cardiac efficiency, without heart rate change (24, 25), but high adrenaline levels greatly decrease efficiency (11).

It would seem to be worth studying the rôle of chemical effects of the agents causing increased heart rates upon the work capacity of the heart, in relation to the problem of fitness. A high concentration of an agent like adrenaline in heart muscle might set certain metabolic processes at such a rate that the desirable approach to the recovery condition is not maintained. The heart muscle in life never fully recovers from contraction in the sense that skeletal muscle does, but it must nevertheless be maintained at a certain position approaching full recovery in order to carry on efficiently. This position can apparently be altered by adrenaline. Whether such changes are responsible for fitness levels would seem to warrant study.

5. *The effort syndrome.* In every major conflict since the American Civil War attention has been paid by medical officers to the so-called "effort syndrome" first fully described by Da Costa (26). Various names have been applied to the condition, and the fact that the disorder is not specifically limited to fighting men has been pointed out since the first report. Nevertheless it is commonly held that emotional strain in persons in general ill-health and/or with constitutional factors disposing to the disease is a precipitating factor.

Numerous recent reviews have discussed the known facts in connection with this disorder (27, 28, 29, 30). The most comprehensive review (31) comes to no conclusion as to the basic functional disturbance. Many of the symptoms can be simulated by hyperventilation and certain investigators (32) conclude that hyperventilation alkalosis is the cause of the other symptoms. However these workers neglect the fact that in their own cases the pathological effects of hyperventilation occur at a much lower pH in their effort syndrome subjects than in their normals. Consequently it is obvious from their own data that some difference besides hyperventilation exists between the two groups.

Other workers (33) have shown in a similar group of subjects that the arterial oxygen saturation is from 4 to 10 per cent below normal in effort syndrome. These subjects frequently showed a Cheynes-Stokes type of respiration indicative of central anoxia. Frequent sighing also occurs in this disorder. It is difficult to reconcile low arterial oxygen saturation with hyperventilation, although it is possible that with excessive aeration of parts of the lungs, combined with poor aeration of certain other parts, the mixed arterial blood could have a low carbon dioxide content and a high pH. This is true because the alveolar carbon dioxide tension can be lowered relatively more than the oxygen tension can be raised by increased aeration of the lungs. Consequently if, for example, 80 per cent of the lungs were over-ventilated and 20 per cent were not ventilated at all, one could obtain approximately the observed low oxygen saturation and the low carbon dioxide tension in the mixed arterial blood. It should be pointed out, however, that the oxygen saturation and carbon dioxide studies were made on different subjects by different investigators.

The heart is the focal point of symptomatology in effort syndrome. Practically all patients complain of palpitation on slight exertion and many evidence pain and discomfort referable to the heart. It is, however, virtually certain that there is no primary disorder in the heart. Consequently a more basic cause for the total syndrome presumably exists.

In some way the pathological processes in effort syndrome affect the function of the heart. It is very unlikely that small decreases in blood oxygen or increases in pH could be responsible for the

observed cardiac symptoms. It seems possible that persistent changes in autonomic nervous system influences could cause the condition. It is not likely that a simple increase in sympathetic stimulation occurs because tachycardia is not consistently present, but there might easily be increases in both sympathetic and parasympathetic discharges, which would leave the heart rate constant, and yet allow the adrenaline to exert unfavorable metabolic effects on the heart muscle. Such an hypothesis would be in harmony with the prevalent clinical impression that externally imposed emotional factors are important etiologically, along with constitutional tendencies toward emotional instability. Apparently no attempts have been made to simulate the effort syndrome in animals or man by the chronic use of agents such as adrenergic and cholinergic drugs.

6. *Conclusions.* Cardiac function cannot safely be ignored in the general problems of convalescence from diseases which do not primarily affect the heart. The rate of onset of cardiac failure is a critical factor in determining death or survival in a variety of conditions such as shock, hemorrhage and toxic states.

In assessing fitness for exertion the function of the heart is a central problem. The stroke volume is dependent on energetic factors intrinsic to the heart muscle, as well as upon peripheral vascular and autonomic nervous factors. The ordinary treatment of the cardiac aspect of fitness is much too superficial and has not struck at the basic problem of the ability of the heart muscle to do work. The heart rate changes are secondary to more important basic factors. These primary factors deserve greater attention than they have received.

The effort syndrome comprises a functional disorder in which disturbances in cardiac physiology, although probably not primary, nevertheless appear to play an important part. Existing information does not allow one to trace the nature of the basic functional disturbance, but there is suggestive evidence that abnormal autonomic nervous influences may be primary to several other disturbances. Such influences upon the heart could, if they occur, rather readily account for palpitation, left thoracic pain, limited exercise tolerance, among other symptoms.

This statement has been aimed at two objectives, presenting in general the current state of knowledge about the problem, and second indicating lines of study which seem to the author to be promising. It is very obvious that a wide range of problems awaits study, and there is reason to believe that such research would be rewarding in basic information and useful results.

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CIRCULATORY ADJUSTMENTS: THE PERIPHERAL CIRCULATION

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In considering the physiological state of the peripheral blood vessels during recovery from disease or injury, it must be recognized at once that the term convalescence, as usually used, includes a wide variety of completely different conditions. Thus, a group of young soldiers, though initially in good physical condition, will as individual patients in their convalescent period present completely different peripheral circulatory problems. These will depend upon the site, nature and seriousness of their wounds, as well as upon the operative treatment required. Even during recovery the reactions of the peripheral vessels will be influenced by the amount of blood lost, and by the promptness and completeness with which plasma proteins and erythrocytes have been replaced either by intravenous administration or by the patient's own tissues.

Prolonged exposure on the battlefield to thirst and heat severe enough to produce vascular collapse, or to cold severe enough to produce frostbite, often leave the vasomotor system and the peripheral vessels abnormally vulnerable to extreme changes in environmental temperature for weeks or months afterward. Injury to nerves, secondary infections, and nutritional difficulties during the operative period or during intercurrent disease also affect vascular function for prolonged periods. Excessive vasoconstriction in response to emotional disturbances, while seen most clearly in Raynaud's disease, occurs also in milder and less dramatic grades so that weakness and anxiety of the convalescent patient may produce functional vascular abnormalities. Moreover in the older age groups, even within the range of 35 to 45 years, early degenerative changes in the vascular tree make sweeping generalizations unsatisfactory in solving difficult individual problems.

For these reasons consideration of the peripheral circulation in the recovery period should avoid all tempting diagnostic rules of thumb and particularly should avoid therapeutic regimentation. It follows with equal force that this discussion can include only a brief description of several fundamental distortions of vascular physiology common to illness in general. In essence convalescence is merely a stage of the causative disease or injury and it is as impossible to consider under one heading the manifold peripheral circulatory disturbances of all convalescent patients as it would be to describe together as one topic the pathological physiology of immersion foot, shock and pneumonia.

It is probably for this reason that the literature is relatively barren of studies dealing with the peripheral circulation in convalescence as such. In fact the few papers available on the general subject appeared during or immediately after the first world war and, as in the present war, obviously arose from the necessity of hastening return of soldiers to the front or civilians to their work. As would be expected under these circumstances objective observations and tests are few, conclusions being based largely upon the general effects of a set regimen on days of hospitalization for groups of patients.

Bridgman, for instance, in the last war studied the length of convalescence by testing performance in three stages of graduated exercises, the most advanced stage consisting of 40 minutes of steady setting-up exercises, one hour of squad drill, and a 5-mile hike. Tested in this rigorous fashion, which is certainly appropriate for soldiers about to be returned directly to full duty, the effects of infection or operation last longer than is generally assumed in civilian practice. The average patient recovering from mumps was able to perform the full schedule of exercises about 5 weeks after onset of the disease; for pneumonia recovery required 8 weeks; scarlet fever 11 weeks; tonsillitis and sinusitis 5 weeks. Follow-up of 2000 cases showed, however, that 99 per cent fulfilled regular duties immediately after discharge. Since physical exercise is a test of peripheral circulatory adjustment as well as cardiac and respiratory function, it would appear that completion of convalescence in a military sense requires a more adequate recovery and greater efficiency of vascular coordination than is demanded in civilian life where it is possible to discharge the convalescent patient with a vague recommendation to "take it easy for a month or two; let me know if you have any trouble and come back for another examination in 3 months."

If there is one common factor in all convalescence, it is that during its initial stages the patient changes his position from recumbency to sitting, standing, walking and finally working. In the recumbent position the peripheral blood vessels and heart are at about the same hydrostatic level. The blood pressure in the venous capillaries, though but slightly higher than that in the large central veins, supplies in recumbency ample *vis a tergo* to ensure adequate return of venous blood to the heart. Hemorrhage, shock and infection having been treated successfully, the peripheral circula-

tion of the patient may be quite adequate for the very minor demands of the recumbent position. Latent weakness can still be present and become apparent only when the patient attempts to get out of bed and to assume the erect position. At this time the hydrostatic disadvantage of sitting or standing requires immediate adjustments on the part of the vasomotor system and peripheral circulation. Tardiness or incompleteness of adjustment leads to faintness, "giddiness," dimness of vision, tachycardia, palpitation, deepened respiration, weakness and, if these signals of imminent cerebral anemia go unheeded, unconsciousness with a few convulsive movements, localized or generalized.

The administration of the vasodilator drug, sodium nitrite, to healthy young subjects produces a similar weakness of the peripheral circulation, which is latent in recumbency but quickly obvious on standing. Weiss and his coworkers found that in the recumbent subject sodium nitrite did not produce symptoms, affect venous pressure or reduce venous return to the right heart. Yet the tone of the venous and capillary systems was reduced as shown by a 20 to 40 per cent greater increase in limb volume during passive congestion. Standing revealed this weakness more clearly by producing syncope owing to distension of the vessels below the heart and a rapid fall of venous pressure in the lower extremities to levels lower than the hydrostatic pressure required to return blood to the right heart. The vasomotor system, however, remained active; the high diastolic pressure at the moment of collapse indicated heightened, rather than lessened, arteriolar tone. The responses of the peripheral vessels to pinch, deep respiration and to cold persisted. By exclusion the circulatory failure was ascribed by Weiss to diminished cardiac output resulting from the stagnation of blood in the relatively lax or atonic capillaries and venules in the dependent parts of the body. The critical importance of heightened venous pressure in revealing the greater distensibility of these vessels is indicated by the absence of symptoms in recumbency and their prompt appearance in standing. Failure of this type was more likely to occur in warm environments and less likely to occur in the cold. Epinephrine and pitressin did not protect against this postural action of nitrite, but paredrinol, which contracts venous reservoirs, relieved the symptoms of some subjects though not others.

No sharp line of demarcation separates the normal from the abnormal in this respect. In susceptible subjects particularly with hypotension the same sequence is observed in warm weather, on first arising in the morning, or on resuming activity after a day or two in bed. Normally the carotid sinus mechanism and the vasomotor system adjust vascular tone to new conditions reflexly within a few seconds and cerebral anemia is relieved after a very brief period of "giddiness" or "going black."

In the convalescent patient, however, reeducation and training may be necessary at first because infections such as colds and sore throat, dehydration, blood loss, fever and fatigue all delay and enfeeble these adjustments. The potential degree and persistence of this enfeeblement has been illustrated by studies on the effects of simple fever, produced by heat cabinets or typhoid vaccine for several hours, and therefore uncomplicated by underlying infection. Such fever leaves a residue of maladaptation for some time even after body temperature has returned to normal.

Kopp observed after artificial fever a greater incidence of immediate or sustained fall of systolic blood pressure, more frequent fluctuations of blood pressure above and below the initial level, inability to maintain an initial rise in systolic blood pressure, a fall in diastolic pressure, or inability of diastolic pressure to rise, greatly reduced pulse pressure and a greater or progressive increase in pulse rate. The symptoms observed in sitting and standing included dizziness, eructation of gas, restlessness, dyspnea, nausea, weakness, blurring of vision, syncope and in some instances convulsions. These symptoms were more frequent and more marked in patients over 50. He considered the responsible factors to be dehydration, vasodilatation in a warm environment, early organic vascular disease and "exhaustion of the sympathetic nervous system." Lack of any direct relation between symptoms and the grade of hypotension precluded establishing any critical blood pressure level. Responses also differed in the same patient from day to day so that the convalescent should be excused for inconsistencies in his symptoms. Like the symptoms of nitrite action, however, those of the post-febrile period were immediately relieved by recumbency.

Related to these common disturbances of the peripheral circulation in early convalescence are the slightly decreased circulation time in fever (Wollheim and Lange) or after operations (Bellis et al), and the temporary but marked diminution of cardiac output for 1 to 4 days postoperatively (Snyder). Less certainly relevant to war injuries, but nevertheless suggestive, is the finding that smoking produces less constriction of the peripheral vessels in patients recovering from cardiac failure than in ambulatory subjects (Cates and Giovanaszzi).

The adjustments to physical exercise depend only partly on the peripheral vessels but the observations of Mann indicate the period required for complete recovery even after fever and active infection have disappeared. Thus, after pneumonia the ability of convalescent patients to adjust to

exercise, as measured by their blood pressures after graded work, was slow. From 8 to 17 days without fever were required for return of maximum work tolerance. The behavior of blood pressure during graded work in this series was a more sensitive indicator of progressing convalescence than was the pulse rate.

Studies of this kind, though suggestive, are still fragmentary and cover only a few of the many situations met with in a convalescent hospital. A systematic survey is needed, with emphasis on the use of modern objective and quantitative methods of studying the peripheral vessels. Such a survey would supply information to supplant vague generalizations and would reveal differences related to the underlying disease. These studies should logically begin with observations on normal subjects who are simply confined to bed, proceed to normal subjects confined to bed and given artificial fever, and then to patients with infection and fever, simple operations, trauma followed by simple hemorrhage, by shock, by operations and by special complications. It has been claimed that continued stimulation of the vasomotor system by raising the head of the bed 8 to 12 inches at night tends to relieve the symptoms to postural hypotension, but the usefulness of these and other medical measures in the recovery of normal vascular reactions while still in bed during convalescence has not been explored satisfactorily.

As a second fundamental principle it must be emphasized that the functional effectiveness of the peripheral circulation involves more than blood vessels, their innervation and their reflexes. Return of venous blood from the peripheral vessels depends upon intra-abdominal and intra-thoracic pressures and, particularly in balanced standing or walking, is hastened by the "muscle-pump" working in association with the venous valves. The importance of avoiding stasis in the lower extremities of bedridden patients, by means of deep breathing exercises and graded calisthenics in bed, is well established. Such muscular movements reduce significantly the incidence of postoperative thrombosis and pulmonary embolism.

To this mechanism Henderson suggested adding a less obvious but more continuously acting peripheral circulatory aid, termed by him variously as "muscle tonus, intramuscular pressure or the venopressor mechanism." Tissue pressure, measured directly by a needle inserted into the belly of biceps muscles of patients in bed, is lower than that of healthy young men. It is apparently lowered by overbreathing, illness, hemorrhage, shock, dehydration, anesthesia and operations. It can vary widely from muscle to muscle and can be increased by muscular contraction, carbon dioxide inhalation, coramine, small doses of metrazol, adequate fluids and, according to Henderson, by small amounts of strychnine. Mateeff and Petroff have described the deleterious circulatory effects of grossly lowered muscle tone in Parkinson's disease, muscular dystrophy and peripheral neuritis. Relief of symptoms on standing was obtained in some of these patients by applying elastic bandages to the lower extremities. Mayerson and Burch found that normal subjects who do not develop syncope usually show a more marked increase in "intramuscular pressure" when standing, while those who show circulatory embarrassment do not show this increase.

It is still difficult to distinguish cause and effect with certainty in this association because more adequate filling of the peripheral vessels by distant constriction, e.g. in the splanchnic region, might simultaneously increase venous return to the heart and improve resistance to standing. Simultaneously, venous filling and venous pressure being greater in the extremities, the tissue pressure might conceivably increase secondarily in muscle bundles enclosed by relatively inelastic fascial sheaths.

Whether or not the mechanism is as simple and as completely peripheral as Henderson describes, the general concept gains considerable support from the value of early supervised exercises performed by patients while still in bed, and followed by the programs of calisthenics and "physical reconditioning" now established in many civilian and military hospitals (Rusk, Reid). These measures, associated with mental reeducation to reduce anxiety and boredom have reduced hospital readmissions, sick leaves, and relapsing illness of convalescents en route to home or camp. They have also increased the ability to perform full duty at once when patients are returned to heavy, routine training schedules.

Assignment of such exercises and urging or commanding their performance places, however, upon the physician an additional burden of responsibility which he does not need to assume when patients are allowed spontaneously to do only as much as they feel impelled, or able, to do without specific recommendation. Such assignments require careful estimation of the adequacy of the peripheral circulation at each stage of convalescence. It has been emphasized previously that convalescence is a part of each disease, not a syndrome per se. Each patient will therefore present in addition special problems depending upon past history, as well as upon medical, surgical, nutritional, neurological and psychological complications. Under these circumstances, and particularly in prolonged convalescence, it is essential to avoid the temptation of regimenting daily programs according to a rigid routine. Even in a field as restricted as the peripheral circulation, if the temptation of adhering to "routine measures" is not resisted the unquestioned beneficial effects to the majority will be more than nullified by the injury done to the minority.

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NEUROMUSCULAR DENERVATION, ATROPHY AND REGENERATION

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This report will include a brief description of the changes that occur in skeletal muscles following the loss of their nerve supply and of the changes that take place in these muscles when they undergo regeneration subsequent to reinnervation. A somewhat more detailed account will be presented of measures which have been employed for the purpose of facilitating recovery from peripheral nerve injuries. Unless otherwise specified "denervation" as used here, refers to a complete traumatic separation of the axones in peripheral somatic nerves. Most of the information concerning atrophy and regeneration has been drawn from the results of animal experimentation. There is a paucity of information concerning these phenomena in man.

Morphologic changes. An excellent account of the morphologic changes in muscle following denervation has been reported by Tower (1). The gross changes consist chiefly of a reduction in the size and weight of the affected muscles. The relationship of the rate of weight loss in the denervated gastrocnemius muscle to time conforms to the equation for a reaction of the first order (2). Sufficient data are not available to allow comparable calculations of atrophy rates in the human and other muscles in animals. According to most observations different rates of denervation atrophy occur in different muscles. It is possible that a careful study of the rates of atrophy of different muscles might reveal information concerning the fundamental causes of atrophy.

Microscopic studies reveal a number of important and interesting alterations. The earliest and most conspicuous change is one involving a loss of cytoplasm from the muscle fibers. There is some evidence to indicate that the sarcoplasm is lost sooner or faster than the myofibrillar substance. A remarkable preservation of the cross and longitudinal striations occurs for a considerable period of time after denervation and the end-plates, on the whole, show relatively little atrophy. Both the extra- and intrafusal fibers undergo comparable atrophic changes. There appears to be an increase in the number of nuclei as atrophy progresses but it is not clear to what extent this is due to an increase in total number of nuclei per muscle or to a concentration of the original number within smaller muscle fibers. The same uncertainty exists over the question of whether the increase in connective tissue represents a condensation of that originally in the muscle or whether new connective tissue has appeared. The studies based on analysis of muscles in different degrees of atrophy for sodium, collagen, chlorides and water suggest that the major part of the increase can be attributed to relative rather than absolute changes. A late change after denervation can best be described as degeneration and accounts for the loss of a variable but relatively small mass of the muscle. The end result of denervation atrophy appears to be the disappearance of tissue recognizable as muscle and the presence of fibrous tissue as the dominant structure. It has been established (1) that the above mentioned gross and morphologic changes

which occur when a peripheral nerve is severed are due to the loss of motor-nerve relationships and are not appreciably modified by the concomitant loss of autonomic and sensory innervation.

Chemical changes. Skeletal muscle undergoing denervation atrophy exhibits numerous changes in its chemical composition (3). None of these changes are specific effects of denervation inasmuch as similar alterations are found in atrophies resulting from causes other than denervation. Many of the changes in the concentration of muscle constituents are attributed to alterations in relative amounts of muscle cell and non-muscle cell phases. The latter is represented by the extracellular spaces, connective tissue, nerve and blood vessel structures. During atrophy the relative mass of the former progressively diminishes and that of the latter increases so that an analysis of an atrophic muscle reveals a higher concentration of the substances that are contained exclusively or largely in the non-muscle cell phase. This accounts largely for the increased concentration of fat, collagen, sodium and chloride. On the other hand, substances confined chiefly to the muscle cells such as total acid-soluble phosphate, adenosine triphosphate, creatine, and potassium show a decrease in concentration because of a relative diminution in the mass of muscle cell substance. For a considerable period of time after denervation there occurs no marked change in the concentration of most of the constituents peculiar to the muscle cell. A marked drop in glycogen concentration is apparent as early as 48 to 72 hours after denervation. The magnitude of the glycogen changes are such as to exclude phase changes as being accountable for any appreciable portion of such losses.

The "in vitro" use of oxygen by denervated muscle has been found by a number of investigators to be either unchanged or slightly increased when expressed on the basis of calculated muscle cell phase. The results of studies upon oxygen utilization "in vivo" have been undecisive and conflicting, chiefly owing to the difficulties of making accurate measurements of blood flow. The studies on enzyme concentration and activity in denervated muscle are fragmentary. It is not clear whether the changes that have been reported are the result of atrophy or pertain to its causation.

Functional changes. A number of characteristic functional changes are exhibited by muscles undergoing denervation atrophy. It has long been known that denervated muscle exhibits an increased sensitivity to galvanic stimuli and a reduced sensitivity to faradic shocks. The often quoted statement that denervated muscle loses entirely its sensitivity to faradic current refers only to conditions in which the stimuli are applied through the skin. More effective application of such stimuli to the exposed muscle will elicit a response as long as the tissue possesses contractile properties. Denervated muscles show a marked lengthening of chronaxie, a change which has proven to be a reliable diagnostic index for the presence of the denervation and reinnervation states. The twitch response of denervated muscle is slower and more prolonged than that of normal muscle. Measurements of maximal strength show that muscles undergoing atrophy are weaker than normal control muscles. The loss of strength is due in part to the presence of a smaller mass of contractile tissue, and in part to an impaired functional state in the contractile mechanisms of the muscle cell.

Intravenous injections of acetylcholine will evoke a contracture response in denervated muscles shortly after the severed nerves lose their excitability. Muscles undergoing atrophy during the atonic periods following an upper motor neurone lesion and during immobilization by joint fixation (4) also exhibit an increased sensitivity to acetylcholine but the thresholds of sensitivity are much higher than those for denervation atrophy.

The loss of motor nerve is followed by the appearance of fine fibrillary contractions in the muscle. These contractions make their appearance soon after the degenerating nerve loses its excitability and persist as long as the muscle retains contractile properties. They appear to be asynchonous contractions of either the fiber as a whole or a portion of its structure and fail to cause the development of any appreciable amount of tension by the muscle. It is believed that denervated muscle becomes sensitized to some substance in its environment. Acetylcholine and potassium have been suggested as agents responsible for the excitation of fibrillary activity. In any case the appearance of this fibrillation is generally coincident with an acceleration of the degenerative changes in the muscle.

In many instances denervated muscles have been observed to develop a static contracture or permanent shortening which is gradually lost upon reinnervation. It is not clear to what extent this condition is due to an actual shortening of the muscle fiber per se or to the effects of attending fibrosis in tendons, fascia and joints.

Following the severance of a peripheral nerve there occurs a vasodilation from loss of vasoconstrictor control which allows for an increased blood flow through the paralyzed muscles. Later there occurs a recovery of a portion of the vascular tone and a sensitization of the smooth muscle to certain substances in the blood and lymph. It is not known to what extent the individual components of the vascular bed are affected in the different stages of atrophy. Uncertainty exists as

to the effects of fibrosis on the exchange of material between blood and cells.

Re-innervation and regeneration. At the onset of functional motor reinnervation the progress of atrophy is arrested and muscle regeneration is initiated. All muscle fibers are not simultaneously reinnervated and some are destined never to re-establish neural contacts. Thus, for a variable period of time, atrophy and regeneration are concomitant states in the same muscle.

The phenomenon of nerve regeneration presents several interesting stages. The first is concerned with the growth of nerve tissue which serves to bridge the gap and reunite the peripheral and central stumps. This is accomplished by axone processes from the latter. Two conditions are essential for optimal bridging of the gap. One is the presence of a proper surface or interface for the guidance of the sheath cells and nerve fibers. The other is a scarcity of scar tissue which offers an impediment to orderly growth and results in dissipation through branching, straying, blocking or strangling. The detailed accounts of the surgical techniques which are employed to reunite the ends of severed nerves are beyond the scope of this report. It is pertinent, however, to refer to the use of plasma fibrinogen sutures (5), neural grafts and arterial sleeves (6) as effective measures for promoting reunion of peripheral and central stumps. These techniques offer promise of allowing for an earlier and more complete reinnervation than is possible with stitch sutures.

Adaptations for the reception of the budding axone processes have already been made by the time of their arrival at the peripheral stump. These consist in part of a degeneration and phagocytic removal of the myelin and axone structures of the severed fiber and an organization and proliferation of the Swann cells. Under the guidance of the Swann tubes the flow of axoplasm is directed toward the peripheral structures. The pathways which are destined to be followed by regenerating motor and sensory processes appear to be largely determined by chance. Calculations reveal the rate of growth of the axone tip is not appreciably different in sensory and motor axones and that there is little difference between the rates of growth in man and those in the dog, rabbit and rat. Moreover the rate of outgrowth is but little influenced by the length of the pathway and the age of the animal. The rate of forward advance of the axone tips has been found to be of the order of 3 to 5 m.m./day. In most instances the appearance of myelin lags but little behind axoplasm outflow. The newly regenerated axone must undergo anatomical and functional maturation before regeneration is complete. The newly formed processes are of small diameter and conduct impulses at slow velocities (7).

Upon arrival at the muscle fiber the regenerating axone tip makes contact with the sarcoplasm of an end-plate and after a short delay some degree of function is restored in the newly established neuromuscular relationships (7). Many fine terminals of axones miss the old end-plates and contact muscle sarcoplasm at other points which soon develop into new end-plates. Other terminals may fail to establish sarcoplastic contacts. Eventually sensory fibers which have followed old motor axone passage-ways degenerate and disappear. A similar fate seems to befall in most instances all but one motor axone whenever reinnervation of a muscle fiber by more than one axone occurs. The success in establishment of motor end-plate contacts depends upon the extent of atrophy existing in the muscle (8). It would appear as if fibrosis constitutes a barrier to the formation of successful contacts. This fact points to the importance of an early and effective reunion of the peripheral stump in order to facilitate early reinnervation and possibly to measures that may be taken to retard muscle atrophy prior to reinnervation. Even under the most favorable conditions reinnervation is incomplete and some muscle fibers are destined to undergo final atrophy and degeneration. The degree of failure is greater in cases where reinnervation is delayed and atrophy has progressed to an advanced degree. Remarkable instances of reinnervation and regeneration have, however, been reported for clinical cases after long-delayed nerve suture but the exact limitations of such possibilities have not been fully explored. Numerous attempts have been made to divert the bifurcating processes of regenerating axones to muscle which have permanently lost their original motor innervation. Some investigators report favorable results following such procedures while others regard their results as negative. Much more work must be done before it is possible to evaluate the practical significance of this mode of reinnervation.

Attempts have been made to calculate the overall rate of regeneration in peripheral nerves in man (9). This has been done by dividing the estimated distance of the nerve lesion from the muscle by the time elapsing between the injury and the first reappearance of voluntary contractions in the affected muscles. The average rate of recovery has been found to be about 1.5 m.m. per day. In spite of the numerous variables that must enter into such estimations it would appear as if such calculations might offer valuable prognostic aids.

The recovery of mass and strength by regenerating muscle follows a fairly regular course if optimum conditions for reinnervation are provided (10). Inasmuch as some fibers fail to become reinnervated even under the most favorable conditions, some degree of permanent atrophy is to

be anticipated after nerve injury. Following reinnervation the muscles rapidly recover strength. The rate of strength recovery closely parallels that of muscle mass. It is due in part to an increase in size of the muscle fibers and in part to a recovery in the tension-producing capacity per unit mass of the muscle fiber. This recovery of strength is not paralleled by return of functional coordination (5). A muscle reinnervated from axones originally belonging to another muscle group continues to respond in phase with the latter. Many animals possess little or no capacity for reeducation and readjustment to such abnormal situations. In man it is claimed that some readjustments can taken place but the possibilities appear to be limited.

The fibrillary activity ceases promptly after reinnervation. The contracture response to acetylcholine disappears later and more gradually. There is little information concerning the chemical composition of regenerating muscle. There occurs an increase in the creatine concentration by amounts which are commensurate with the relative increase in muscle cell phase. The onset of reinnervation is accompanied by a rapid restoration of glycogen concentration to normal or above-normal values.

Conditions affecting rates of atrophy and regeneration. Numerous investigations have been undertaken to determine the effects of various conditions upon rates of atrophy and neuromuscular regeneration. Such measures have evolved largely from preconceived ideas concerning the fundamental cause of atrophy. The results of such studies have not always been consistent or conclusive. In this connection it should be pointed out that, where rates and extent of atrophy are estimated from the differences in weights of denervated and contralateral control muscles, valid conclusions can only be drawn if the experimental procedure itself exerts no appreciable effect upon the control member. It is important, therefore, to be sure that changes in the control muscle due to such conditions as growth, inanition and toxemia either were avoided or duly evaluated before attempting to draw conclusions as to the efficacy of any procedures.

Langley (11) suggested that the weight loss seen in denervated muscle represented an overwork or exhaustion atrophy caused by the continuous fibrillation. The repeated administration of large doses of quinidine and atropine causes the abolation or inhibition of fibrillary activity without retarding the loss of strength or weight in the denervated muscles. In addition, the administration of atropine fails to exert any beneficial effect upon neuromuscular regeneration. On the other hand another group of drugs, including acetylcholine, mecholyl, potassium and prostigmine, enhance fibrillary activity without appreciably affecting rates of atrophy. It seems possible that a drug might be without effect upon the rate of muscle atrophy and regeneration and yet exert a beneficial effect upon the functional maturation of the regenerating tissues.

Attempts have been made to alter the course of atrophy through changes in the levels of vitamin intakes. Acute withdrawal of vitamins E and the B-complex group proved to be without significant effect upon the rate or extent of neuromuscular regeneration. The regeneration of muscle following reinnervation was found to be somewhat slower in guinea pigs subsisting on intakes of vitamin C recognized as suboptiminal for the organism as a whole. In the rat neither biotin deficiency nor excess intakes of biotin affected the rate of neuromuscular regeneration. The effects of anorexia and chronic inanition associated with subnormal intakes of some vitamins must always be evaluated before drawing conclusions as to the rôle of vitamins. The information at hand should not be interpreted as evidence that vitamins are unnecessary for regeneration inasmuch as significant amounts are available from storage and bacterial sources, but rather that states of acute inanition and low vitamin intake can exist for considerable periods of time without appreciably effecting the state of regeneration. Moreover the results of experiments on neuromuscular regeneration in animals have shown that excess intakes of vitamin B-complex group, ascorbic acid, biotin and alpha-tocopherol were without effect upon the velocity or extent of neuromuscular regeneration. It would appear that the level of vitamin intakes recognized to be adequate for the organism as a whole are also adequate for optimum recovery from peripheral nerve injury.

Much evidence has been found to indicate that atrophy results from the absence of tension development by denervated muscle. Rates of atrophy comparable to those following denervation occur after tenotomy and during immobilization. These are conditions where neural contacts are preserved but a lack of tension development exists. Furthermore electrical stimulation provides an effective means of delaying atrophy only if it is done under conditions which result in effective tension development by the muscle. The rate of atrophy following tenotomy is not retarded by electrical stimulation. In this condition the muscles contract but fail to develop appreciable tension during stimulation. It has been suggested that the energy levels and metabolites established by the chemical reactions associated with tension development may be necessary for essential anabolic processes in muscle. It is possible also that a certain amount of tension is required to maintain the proper alignment of the molecular

patterns in the submicroscopic structures of muscle.

Immobilization of a denervated limb by braces or casts has been found to be without effect upon the rate of denervation atrophy (12). This may be due to the fact that denervation alone permits the maximal degree of tension loss and inactivity. However, when the state of immobilization is maintained after the onset of reinnervation there occurs a retarded rate of recovery of weight and strength by the regenerating muscles. Thus it would appear as if the deleterious effects of immobilization are related not to greater rates of atrophy after denervation and slower nerve regeneration but rather to a failure of the reinnervated muscles to undergo regeneration in the absence of tension. In addition, immobilization of a limb leads to atrophy in the non-denervated muscles.

Considerable controversy exists as to the efficacy of electrical stimulation in the retardation of atrophy. It would appear as if many of the negative results were due to a failure to employ stimuli of sufficient strength to cause strong muscle contractions. Electrical treatment with shocks too weak to cause strong contractions have proven to be ineffective. Another variable must be considered, namely the degree of stretch existing in the muscles during the time of their treatment. If a denervated muscle is weighted during the treatment period, the effects of electrical stimulation are much more pronounced than when less favorable conditions for tension development are allowed. Although it is possible to retard atrophy by electrical stimulation, it is impossible to prevent a gradual decline in the strength of denervated muscle (13). That is, the treated muscles are stronger than their untreated denervated controls but the increase in strength is due a greater quantity of contractile tissue rather than to any improvement in functional quality. It was found that when the techniques of stimulation which had proved to be very effective in retarding the atrophy of denervated muscles were applied to normal muscle they very frequently caused some degree of atrophy and loss of strength. This observation suggests that it may be a fallacy to transfer techniques found effective for totally denervated muscles to the treatment of regenerating and partially paralyzed muscles. A problem exists to find a non-injurious stimulus pattern which will be tolerated by the patient and still be effective in retarding atrophy and facilitating regeneration of muscle. It should be remembered that delay in atrophy can only be of aesthetic value unless the muscle subsequently undergoes functional reinnervation.

It is apparent that the information established largely from animal experimentation is, indeed, meager and incomplete. However, it is hoped that some facts and suggestions may be gleaned which will prove to be useful in the management of clinical cases of peripheral nerve injury.

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GASTRO-INTESTINAL FUNCTION DURING CONVALESCENCE

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That the functions of the gastrointestinal tract are subject to derangement as the result of disorders in almost every other system of the body is readily apparent and well-known. Similarly, diseases arising primarily in the digestive tract frequently affect the function of portions of the alimentary canal other than those immediately involved in the pathological process. It is not, therefore, surprising that many of the problems which arise in the course of convalescence from a wide variety of diseases are referable to the digestive system.

Such secondary gastrointestinal malfunction arises mainly from viscero-visceral and somato-visceral reflexes. Thus, for example, a ureteral calculus may cause "dyspeptic" symptoms or dyskinesia of the colon, and pain arising in almost any part of the body inhibits gastric tone and motility. In addition the digestive functions may be disturbed by an altered blood chemistry or endocrine balance; thus "constipation" is a common symptom in hypothyroidism. Finally circulatory disturbances or the anoxia of severe anemia may alter gastrointestinal activity; the gastrointestinal complaints occurring in cardiac decompensation are a familiar example. These secondary gastrointestinal manifestations are among the most common symptoms of disease anywhere in the body. Frequently they outlast the disease which gave rise to them; they then become problems in convalescent care.

As regards gastrointestinal functions, convalescent patients may be classified into two broad groups. The *first group* consists of those patients who are recovering from diseases primary in systems other than the gastrointestinal tract. A large number of these patients will present gastrointestinal problems during convalescence, some will not. The *second group* consists of those patients who are recovering from gastrointestinal diseases. The majority of these patients will demand special attention to gastrointestinal function during convalescence.

An attempt to analyze and classify the gastrointestinal problems peculiar to convalescence meets with certain obstacles. Pepper (1) has recently emphasized "a lamentable lack of real factual knowledge concerning the conditions which exist in the convalescent individual himself." Furthermore, since so little is known about convalescence in general, an even greater paucity of knowledge exists about the variations of the convalescent picture in specific diseases. Boas (2) has pointed out that the limitation of the concept of convalescent care to patients recovering from acute illnesses leaves without proper consideration the large group of persons recovering from acute exacerbations of chronic illnesses. It is in this latter group that intelligent convalescent care can exert an important influence in the restoration of the individual to a useful place in the community and particularly in the prevention of a recurrence. There is little question, for example, that adequate convalescent care in the peptic ulcer patient can reduce the probability of an early recurrence.

While it is evident from the foregoing introduction that a completely satisfactory analysis of gastrointestinal function in convalescence must await the accummulation of pertinent data, there are certain manifestations which occur with sufficient frequency in the general run of convalescent patients to warrant special mention and a brief discussion. Among these manifestations or symptoms are anorexia, flatulence, and "constipation." It is immediately evident that such symptoms are not characteristic of convalescence but occur in the acutely ill patient as well as in the patient devoid of a history of acute illness. They are symptoms which may plague the convalescent and physician and must be managed and corrected before the patient can be said to have returned to the healthy functional state.

ANOREXIA. *Hunger and appetite* constitute the complex of sensation which induces, urges, or compels one to seek and ingest food. The two terms should not be used indiscriminately (3).

Hunger in the child and adult is a complex of sensations consisting of general weakness, of abdominal emptiness, and of periods of epigastric tension or distress, which usually, but not always, induce a desire for food. Hunger in the recently born infant or decorticate animal signifies that state of restlessness which is due largely to impulses arising from the vigorous contractions of the fasting stomach and is dissipated by the ingestion of food. Epigastric tension or distress disappears soon after food is ingested, the quantity required being proportional to the initial degree of gastric tension (5). Some normal persons retain a strong desire for food throughout a prolonged fast. Others develop anorexia after a three or four day fast and are bothered by nausea, headache and weakness, which probably are responsible for the anorexia. This point should be considered in convalescence, since, in the presence of good gastric tone, there is certainly no objection to "persuading" the convalescent to eat.

The caloric requirement appears to be the most important factor determining the extent of hunger and the tension and motility of the stomach in fasting. Age is also a factor. The evidence indicates that the decrease in gastric hunger motility with age is related to a decrease in caloric requirement and to biologic ageing of the gastric hunger mechanisms (3, 4). The gastric hunger mechanism is more readily inhibited and for a longer period of time in the aged than in the young adult dog (5).

Many factors inhibit gastric tone and motility. They are too numerous to mention. Any disease usually abolishes gastric hunger motility and gastric secretion when the temperature rises to 102° or 103°F. In the dog recovering from "distemper" the hunger motility may not return to normal until one or two weeks after the body temperature has returned to normal (5). Gastritis and mild infectious states without a rise in temperature depress but do not abolish gastric hunger motility. Hunger motility is depressed reflexly by disease in various organs, by pain (6) and by changes in the chemical composition of the blood (intoxications and cardiac decompensation).

Comment. A consideration of the gastric hunger mechanism in convalescence is important not only because hunger usually increases the appetite, but also because the rate of gastric evacuation is dependent on the tone and motility of the stomach (7). A convalescent patient will tolerate a large meal only if the tone of the stomach is normal. Nausea, vomiting and air swallowing with gastric distension are very likely to occur if the meal is larger than can be tolerated by an "atonic" stomach. A too high concentration of sugar and fat (10% or more in the case of a normal sedentary person) would favor gastric retention by excitation of the enterogastrone mechanism which depresses tone and motility. In our opinion it is inadvisable to provide food too concentrated in fat and sugar or too large in quantity to be well tolerated at one feeding by the hypotonic stomach of a convalescent. Sound physiological judgment is required in ascertaining the most appropriate feeding technique for the individual patient. The most effective management of anorexia in the convalescent is an individual patient problem.

The best means for increasing gastric tone and motility is *physical exercise*. This would indicate that convalescent patients should use their muscles to the extent that is compatible with their condition, but not to the point of excessive fatigue which depresses gastric tone and appetite. A comfortable fatigue is the physiological degree of fatigue.

The most innocuous and best known means of artificially augmenting gastric tone and motility is the administration of *insulin* (8). Insulin (10–20 units 1 hr. before a meal) does not seem to have been used extensively to increase food consumption in convalescence, although several papers attest its value (9, 10, 11). It is well to keep in mind that insulin does not increase gastric tone in the presence of thiamine deficiency (12) and that infectious disease has been reported to increase the need for thiamine (13, 14). More evidence is needed on this latter point.

Thiamine deficiency is associated with anorexia. When the deficiency is complete, a marked depression of gastric tone and motility occurs. When the deficiency is mild, gastric hunger contractions occur but the periods are shorter in duration and the usual tonus rhythm is diminished (15). A daily intake of 0.6 to 1.0 mg. of thiamine has been observed by several groups of investigators to be associated with diminished appetite in normal human subjects (16). However, Keys and his associates (17) have reported no decrease in appetite in normal subjects receiving 0.7 mg. daily for a period of 10 weeks. The exact nature or origin of the anorexia in thiamine deficiency is uncertain. Inasmuch as appetite is a subjective phenomenon and is therefore difficult to control, the extent to which the mild anorexia observed in certain experiments may be due to environmental factors other than a suboptimal intake of vitamin is a moot question. Apparently an experiment has not been performed in which human subjects have been permitted to select at will a quantity of thiamine-free food over a period of weeks or months to ascertain if the quantity of such food consumed will vary with the amount of thiamine administered in capsules. Nevertheless when convalescents manifest anorexia, the possibility that the thiamine content of the diet may be too low for the patient's need should be considered. There is no evidence showing that the addition of thiamine or other vitamins to a diet already adequate will cause an increase in appetite or food intake (18).

One of us (A. C. I.) has observed an increase in food intake after giving patients *prostigmine* for abdominal distension. Whether the increase in food intake was due to the relief from the distension (19) or to the action of the drug on gastric tone and motility is uncertain. No data are available showing that prostigmine in doses (0.25 mg. every 4 to 6 hr.) which cause no undesirable effects and when not used to relieve distension, will augment hunger and food intake.

There is a possibility that in some convalescent patients a type of *anorexia nervosa* may develop which may be related to the intake of only small meals over a period of several weeks. This suggestion is made because dogs with an isolated total pouch of the stomach, if the pouch is not well distended daily, become intolerant to distension of the stomach, probably because the stomach does not manifest normal receptive relaxation (20).

For example, nausea and distress is produced when the stomach is distended with a volume of 100 cc. whereas normally 500 cc. or more is tolerated without symptoms.

Appetite is best defined as a conditioned or learned state of consciousness based solely on the memory of pleasant experiences which are associated with eating and drinking, and creating a desire for food or a special item of diet. It is not appropriate here to discuss the problem of whether "salt hunger," "vitamin hunger," etc., are hungers or appetites.

The fact that hunger may exist without creating a desire for food shows that the cerebral mechanism for appetite is disturbed. The fact that a patient may be in serious physical need for calories or even for salt in the presence of hypochloremia and yet not have desire for them shows that appetite is not a reliable guide in the management of convalescence. To what extent anorexia, when it occurs in convalescent patients, is due to a lack of gastric "tone" or to a disturbance of the appetite mechanism has not been carefully investigated. The consensus is that the anorexia is chiefly due to a disturbance of the appetite mechanism. Yet, we do not know enough about the return of the stomach to normality in the convalescent to be certain that a "psychologic" disturbance is chiefly concerned.

Various forms of appropriate persuasion, suggestion and psychotherapy are usually practiced and are frequently successful when the "Art" is good. "Stomachics" or bitter tonics have been frequently employed for many years to increase appetite. Apparently only one thorough study has been made to ascertain whether bitter tonics actually increase the consumption of food. Moorehead (3) found they did in five hospitalized patients with cachexia and anorexia. Since bitter tonics do not augment gastric motility or psychic gastric secretion in normal patients, they only influence the appetite mechanism, perhaps through gustatory contrast. More evidence is needed; but the available evidence indicates that bitter tonics serve as an adjunct to psychotherapy.

Flatulence. Some convalescent patients are at times disturbed by flatulence, either gastric, colonic or both. Occasionally a patient complains of distension of the stomach in which the stomach does not contain an excessive amount of gas and in which the stomach is hypertonic or the diaphragm is found at a lower inspiratory level than normal and the abdomen protruded, as in vomiting. Such patients believe they are "bloated" when they are not.

It has been conclusively demonstrated (21) that the gas in the stomach is either swallowed air or air aspirated into the stomach. This air, if not eructated, passes to the colon. Colonic gas arises from swallowed air or the fermentation of cellulose or of starch granules which have escaped digestion.

Why the air is swallowed or sucked into the stomach is uncertain. If the esophagus is sectioned and the proximal end fistulized and the lower end closed, vomiting or salivation (a reflex associated with nausea or perhaps subthreshold excitation of the nausea mechanism) does not lead to distension of the stomach with air. Since the action of the superior constrictor muscle of the esophagus normally interferes with the passage of air into the esophagus during inspiration, it is possible that stimuli which decrease the tone of the stomach inhibit the tone of the constrictor so that air is swallowed or sucked into the stomach. On appropriate distension of the gallbladder in dogs, the stomach has been fluoroscopically observed to become distended with air without the occurrence of true swallowing (elevation of the larynx) (23). Cannon and Hedbloom observed distension of the stomach on irritating the cecum (24). When the gastrectomized dog retches repeatedly, the abdomen may become enormously distended. Whether the superior constrictor of the esophagus relaxes as suggested, remains to be demonstrated, but that a loss of tone of the stomach predisposes to the aspiration of air into the stomach is certain. Wilson and Irving (22) have shown that certain positions of the body cause a subatmospheric pressure in the stomach and the same may occur when gastric tone is suddenly decreased.

It is well known that eructation is facilitated by the erect posture. Increased activity and factors which increase the tone of the stomach should assist in the prevention of epigastric flatulence in the convalescent. Activity may be contraindicated in the early convalescence of the cardiac patient, a patient who, perhaps due to poor portal circulation, is frequently disturbed by flatulence. The mechanism of the action of carminatives, when they work, is not settled, though Meyer, Scheman and Necheles (25) found that oil of peppermint speeds gastric evacuation, which indicates an increase in gastric tone.

Though many physicians use in the post-operative and early convalescent patient small doses of magnesium oxide or some other laxative to prevent and treat colonic flatulence (which may predispose to gastric flatulence by reflex inhibition of the stomach), it is established that purging the post-operative patient predisposes to flatulence (26). This is probably applicable to the convalescent, though no published evidence has been found.

Alvarez (26) emphasizes the rôle that "specific food sensitiveness" may play in the causation of flatulence. He found milk to be a prominent offender. Foods such as beans, cabbage, and cauliflower, which are notorious gas formers, should be avoided. Many patients, who for some unknown

reason are predisposed to colonic flatulence when not convalescent, on questioning will report those foods which cause gas in their case.

CONSTIPATION. The objectives are to maintain the caudalward gradient, to prevent impaction and stasis with the consequent reflex disturbances and predisposition to flatulence, and to restore the bowel to normal function. Medicinal irritation is a poor substitute for physiological stimuli.

The general asthenia associated with acute illness and prolonged rest undoubtedly affect the musculature of the colon. Limited food intake associated with anorexia is an important predisposing factor. The use of medicinal irritation or enemata during the preceding acute illness or postoperatively may disrupt the stool habit and develop dependence on an artificial means of producing a bowel movement.

The indicated management is that usually employed for an atonic or hypotonic colon. Physical activity by the patient should be encouraged up to the point of tolerance. This should operate to increase the intake of foods which serve as physiological stimuli. In the selection of foods which provide bulk one has to avoid those which predispose to flatulence. This is frequently difficult to do in practice, and in such cases it may be necessary to omit them and resort to the use of some medicinal irritant or an occasional enema. Theoretically some hygroscopic agent which irreversibly absorbs water and is not fermented or decomposed by bacteria would seem to be ideal; and several such agents are available. However, these agents at times, when used by the convalescent reduce the "space" for food by swelling in the stomach. In such instances, we believe that supplying food is the more important consideration and overbalances the criticism which may be leveled against such a laxative as cascara sagrada or an occasional isotonic saline enema. Otherwise the physiological management of atonic constipation is so well known that further consideration is not indicated here.

SUMMARY

Although much remains to be learned about the physiology of the alimentary tract in convalescence, it would appear that the general objective is to utilize those physiological procedures which promote gastrointestinal tone and motility and to resort to artificial aids as little as possible and only when clearly indicated. According to present knowledge the secretion of the digestive juices do not constitute a significant problem in convalescence except in specific cases. Motor dysfunction is much more likely to be the origin of disturbances in convalescence than secretory dysfunction.

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RESPIRATION IN RELATION TO CONVALESCENCE AND REHABILITATION

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In the broad field of convalescence and rehabilitation the damaged respiratory apparatus poses interesting and little explored questions. However, sufficient information is available to delineate an approach to this problem. The degenerative changes associated with aging and the destructive processes of disease result in a lowering of the respiratory reserve oftentimes necessitating economic and social readjustment. In addition, therapeutic measures may also seriously lessen pulmonary reserve. The large magnitude of that reserve has sometimes made us wasteful in our choice of therapy and has delayed the focus of attention upon industrial respiratory hazards. Even now it probably masks environmental dangers of which we are not aware. The lack of methods sufficiently sensitive to detect small reductions in respiratory ability accounts in a large measure for our difficulty with this problem and constitutes one of the major obstructions to the advancement and application of knowledge in the field of clinical respiratory physiology.

Proper convalescence aims at preserving the largest pulmonary reserve possible. Rehabilitation on the other hand involves a readjustment to environment in order to prevent a further loss of pulmonary reserve, to increase existing reserve, or to adjust the daily breathing requirements to the capacity for breathing. To approach this problem one must not only assess the effect of age, environment and disease (plus therapy) upon the respiratory apparatus but in addition determine the respiratory requirements of the various types of employment.

Adequate ventilation of the blood requires that a sufficient quantity of air be supplied to and properly distributed throughout the lungs, that a normal rate of gas diffusion across the membranes be permitted, that there be unimpeded flow of blood through the alveolar capillaries and that the nerve control of the apparatus be properly integrated. Available space will permit only a brief and incomplete discussion of these factors as observed in the aged and diseased.

The maximum capacity for moving air through the lungs depends upon the patency of the tracheobronchial airway, the resiliency of the structures which must change size and position during breathing, the power and coordination of the respiratory muscles, and the size of the respiratory pump. The voluntary maximum breathing capacity (Atemgrenzwert) introduced by Hermannsen (1) is a far more useful and reliable index of available reserve breathing power than is the vital capacity which is a static measurement and neglects the all important factors of time and coordination. As in other systems, aging reduces resiliency and muscle power thus significantly reducing reserve breathing capacity. Actual destruction of lung parenchyma must be extensive (perhaps one third or more of the total) before it noticeably impairs breathing reserve since the smaller pump will compensate within limits by moving at a faster rate. Hence many patients who have had surgery of the lung or chest wall are not problems of rehabilitation. On the other hand, destructive disease involving the muscles of respiration, the mobility of the bony thorax or the elasticity of the pleura (fibro-thorax) is likely to reduce the reserve breathing capacity. This is due in part to the fact that purely parenchymal disease is usually localized whereas disease involving the bellows mechanism is apt to be widespread. Of greater importance however, is the fact that over-action of the bellows can partially compensate for loss of parenchyma, while the reverse is not true since lung tissue *per se* is passive.

The effects of extensive loss of lung resiliency, improper distribution of air within the lungs and possibly impedance to pulmonary blood flow are classically exemplified by true generalized pulmonary emphysema. In an advanced stage, this disease disrupts every factor of pulmonary function and is extremely crippling. Though ventilation defects do result in an alteration of the blood gases, they seem to make a minor contribution to the disability characteristic of this malady. Actually the earliest, most characteristic and most crippling feature is a reduction in the maximum breathing capacity caused by the loss of lung resiliency and spasm of the bronchial tree. Emphysema of a similar pathological nature may complicate diseases like tuberculosis and silicosis that destroy lung tissue. Fortunately in most such cases the emphysema involves relatively little of the total lung. However, where this complication is widespread and severe both silicosis and tuberculosis may exhibit marked disability.

The breathing apparatus is also crippled by anything that directly or indirectly causes a reduction of the power of the respiratory muscles. This type of impairment is subtle and has not received the attention it deserves. Therapy which limits physical exertion may at times so reduce muscle power that more harm than good is accomplished. For example, in some cases of pulmonary fibrosis or emphysema respiratory muscle

hypertrophy is one of the mechanisms that compensates for the loss of pulmonary resiliency. Treating such cases by confinement to bed or curtailment of physical activity causes muscle atrophy and invites further serious respiratory crippling. At times it is necessary to accept a loss of muscle power in the proper treatment of disease—fortunately the loss is nearly always temporary and with exercise power is regained. It is conceivable that the present trend toward mechanization with its concomitant reduction in physical exertion has robbed man of one of his important compensating mechanisms. The use of exercises directed at increasing respiratory muscle power and improving the coordination of those muscles is to be encouraged.

A priori one might expect unequal pulmonary distribution of the respired air to interfere with effective ventilation of the blood. Obviously a segment of lung, insufficiently ventilated in relation to the volume of venous blood perfusing it, will act as a venous-arterial shunt and may actually cause a lowering of the peripheral arterial oxygen tension and a rise of the carbon dioxide tension. Sonne (2) has demonstrated that distribution of inspired air in the normal lung is not uniform. Roelsen (3) and others have shown that this effect is even more marked in emphysema. In the latter the uneven distribution is apparently severe enough to produce hypoxia and hypercapnia at rest. The rare case has been demonstrated in which ablation of a well circulated but poorly ventilated lung segment has resulted in improved arterial blood gas tensions. Poor distribution can be easily demonstrated in most cases of chronic pulmonary disease but it rarely contributes to disability because usually the poorly ventilated area is also poorly circulated. In some instances the blood vessels are actually obliterated by disease, in others a local vasoconstricting reflex is suggested. Moreover, the low arterial oxygen saturation observed in these cases at rest is nearly always raised during exercise suggesting that the ventilation-circulation ratio can be improved. It remains to be demonstrated that poor lung mixing *per se* plays a very significant part in respiratory disability. However, it should be borne in mind that an adequate maximum breathing capacity may be partly negated by the useless ventilation of a non-circulated segment of lung.

The alveolo-capillary membrane has been implicated in respiratory disability but upon very little actual evidence. Observations of the pathological histology of the lungs in such diseases as silicosis and pulmonary tuberculosis led some to assume that arterial hypoxia should occur in these diseases but actually this is a rare occurrence. The thickening of the alveolar walls seen in both these diseases has little effect, for in the areas that are fibrosed the pulmonary vascular bed is also destroyed. Hypoxia at rest is observed only in far advanced fibroid tuberculosis or conglomerate silicosis and in these cases poor mixing of lung gases is the more logical cause. If thickening of the membrane does lead to diffusion disturbances, exercise should increase the hypoxia with less effect upon the arterial carbon dioxide tension. Such cases have been demonstrated, as for example pulmonary scleroderma and the fibrosis resulting from exposure to irritant fumes. We recently studied such a case, of unknown etiology, whose arterial oxygen saturation was 90% at rest and dropped to 78% during moderately severe exercise. (Oxygen consumption 1835 cc. per minute; body weight 73 kilograms.) Breathing pure oxygen during this rate of exercise decreased his minute volume of breathing from 82 liters to 54 liters. The arterial carbon dioxide content dropped from 38 volumes percent to 28 volumes percent during exercise, showing that only oxygen diffusion was demonstrably interfered with. This man reacted to exercise in every respect as if he were a normal man but working at a high altitude. Such cases are apparently rather rare at present but should irritant gases be used on a large scale in this war, one might reasonably expect the incidence to increase. More precise methods of study, perhaps along the lines of determining the diffusion constant for oxygen and carbon dioxide might be of practical value in these cases.

Before one can rehabilitate an individual whose respiratory apparatus has been damaged it is essential to determine the cause and type of damage and to estimate the respiratory reserve that remains. The cause is usually apparent but it may remain obscure even after intensive study. The structures that have been damaged and the remaining respiratory reserve can be demonstrated by available methods provided the damage is severe enough. The major symptom of respiratory damage is dyspnea or "an awareness of respiratory distress" at levels of exertion previously well tolerated. This is a subjective phenomenon, often but not always associated with the signs of labored breathing. Dyspnea is related to one or all of three factors, namely, the demand for breathing, the capacity for breathing, and the sensitivity of the cortex to sensations of respiratory effort. It has been shown that dyspnea develops when the minute volume of respiration becomes 50–75% of the maximum breathing capacity. The variation in the dyspnea ratio from person to person and even in the same individual from time to time is due to differences in the cortical or awareness threshold. In abnormal states the threshold may be reduced, as for example in the neurotic type of person who focuses his attention upon his breathing and becomes dyspneic at very low levels of exertion in spite of normal breathing response and capacity.

The knowledge that one suffers from chronic disease of the lungs directs attention to breathing and then dyspnea often develops at levels far below actual capacity for effort. Conversely the threshold is sometimes abnormally high in the busy, absorbed individual, who may breathe with difficulty and still not be sufficiently aware of it to complain of dyspnea. It is apparent that other stimuli reaching the cortex may, if strong enough, supersede or may intensify those of respiratory distress. The psychological influence upon dyspnea is extremely important. The factors of dyspnea and the degree to which each is involved can be determined by measuring the minute volume of breathing under the stress of exercise or whatever strain induces dyspnea and relating it to the measured maximum breathing capacity. The resultant dyspnea index

$$\frac{\text{minute ventilation}}{\text{maximum breathing capacity}}$$

is a valuable tool with which to study the respiratory apparatus.

The respiratory response to the demand for breathing can be measured accurately by relating minute ventilation to oxygen consumption. The ratio varies in different individuals and even from day to day in the same person. Nevertheless, the range is narrow enough so that dyspnea on the basis of an abnormal minute volume in response to work becomes very apparent. Available facts suggest that although over-breathing does occur, it is rarely the chief cause of dyspnea at sea level. On the other hand, physical exertion at high altitude produces over-breathing in normal individuals which is a major factor in their dyspnea. This complaint, often encountered among laborers at high altitude is nearly always absent in the same men at sea level. The over-breathing observed during exercise in congestive heart failure, emphysema, fibro-thorax and silicosis offers a rich field for the study of the mechanism responsible for stimulating the respiratory centers. Conclusions from experiments in which only one variable has been changed at a time are difficult to apply to these diseases where nature is changing several variables at one and the same time.

A reduced maximum breathing capacity is the most common cause of dyspnea. The maximum breathing capacity can be determined with a reasonable degree of accuracy, the large personal variations observed reflecting differences in muscle power and coordination. Because of these variations and since the normal value for the diseased individual has rarely been established before his illness, it is difficult to estimate the true reduction in breathing reserve in a given instance. A strong element of incentive enters into this measurement as it does into all voluntary maximum performances.

Efforts at "job analysis" (4) are being made which should be supplemented by actual measurement of respiratory requirements. A large field of useful and practical research is to be found in pursuing the study of correlating a man's respiratory capacity with the respiratory demands of a particular job. The knowledge to be obtained is essential to the proper administration of the rehabilitation problem. Although mechanical methods have greatly reduced the physical effort of the worker, jobs remain which require a fairly high level of energy output either continuously or for short periods. The latter type is more numerous and more apt to be found in skilled trades. Age or disease ultimately reduces the capacity of these men for their jobs because they cannot do the severe work for the short periods; they are still capable however of doing other skilled work. It is now possible to estimate respiratory capacity with reasonable accuracy but very little information concerning the energy and breathing requirements of specific jobs is available.

Two other problems merit attention whose solution would be of unmeasureable value in placing men at suitable work. First, the marked personal variation in susceptibility to "industrial pulmonary fibrosis" must mean in part a varying capacity of the lungs to protect and cleanse themselves after exposure to inhaled fumes and particulate matter. The mechanisms involved would appear to be a field of research within the province of the physiologist that might richly repay intensive study. The second involves the possible association between the strain put upon the organism by respiratory inadequacy and the development of fatigue. Perhaps we have been too concerned with the obvious and dramatic manifestations of respiratory inadequacy and have neglected other more subtle evidences.

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POSTURAL ADJUSTMENTS IN CONVALESCENCE AND REHABILITATION

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There is nothing in the extensive literature on posture indicating that stance adjustments differ qualitatively from the normal in those convalescing from diseases not directly involving the locomotor or nervous systems. Postural adjustments are almost wholly autonomous. They depend pre-eminently on a group of well integrated cord and brain stem reflexes elicited by stimulation of the general and special proprioceptive receptors and cutaneous exteroceptors (28, 31, 32). Alignments thus automatically assumed may be unconsciously modulated in response to afferent impulses received from the telereceptors.

The most distinguishing gross physical characteristic of man is his bipedal mode of locomotion and the ease with which he assumes and maintains the wide variety of vertical postures with which all movements commence and cease. The goal of all standing positions is stability. Balanced postures are attained by readjusting the poise of the head, the curvatures of the segmented vertebral column, and the alignment of the multijointed appendages until the vertical projection of the center of gravity of the body as a whole falls in the neighborhood of the center of the supporting base. Though complex *in toto*, these adaptive adjustments ordinarily require no willed guidance. Indeed, so fundamental is the relation of the center of gravity of the body to the base which supports the whole, that it is little changed by as mechanically disadvantageous events as pregnancy or the carrying of an Army pack (10, 20).

Cortical control of standing supervenes when a deliberate selection of specific positions is imposed upon the subject, as for example, when natural standing is consciously altered to meet the arbitrary ideal known as the military posture. The same may be said of so-called "good posture" or "good body mechanics." Although the esthetic ideal of correct posture is observed infrequently, few have suggested its modification (42). For decades the data from the group studies made on children and adults alike have been skewed toward the low side of scores yielded by a variety of measuring devices (5, 7, 17, 26, 36, 40, 43, 51, 54). The rarity with which "good posture" is seen as a natural phenomenon in man, throws doubt on the validity of the concept.

Relaxed and comfortable standing is nearly indefatiguable (18). It may be maintained for long periods of time with no more discomfort than that incidental to boredom. If uninterrupted for more than an hour, paresthesias of the feet may supervene. When standing fails in the normal healthy individual, it does so not for want of muscular strength or nervous control, but because of inability to compensate adequately for the hydrostatic handicap to the circulation. The sense of weakness and discomfort which is associated with prolonged periods of rigid standing appears to be a pre-syncopal symptom rather than a manifestation of fatigue metabolic in origin.

The nicety with which the mechanical disadvantages of the vertical stance are compensated for is an impressive demonstration of man's power of physiological adaptation. The mechanisms involved are among the most highly integrated and perfectly functioning in the human machine. In spite of these demonstrable evidences of the adequacy of man's protective devices, there are those who assume that the human being is a mechanical misfit doomed to eventual dissolution because of a loosing fight against gravity. Goldthwaite (12, 13, 15), Hooton (22), and Estabrooks (8) are among the most vigorous exponents of this theme. It has colored the whole literature on posture.

All descriptions of good posture prescribe the fullest possible extension of the weight-bearing limbs and vertebral column (21, 33, 49). Particular attention is directed at reduction of the antero-posterior curves of the spine (41, 53). It is not always remembered that considerable variation in the depth of these curves is compatible with normal function (44), and that their acquisition is a part of normal ontogenesis. Their appearance formed one of the most significant milestones in the evolutionary development of the species. The antero-posterior curves give strength and suppleness to the vertebral column. Rogers (41) questions whether reduction of their natural depth can be maintained without constant conscious effort. Relaxation of attention is quickly followed by a resumption of previous alignment characteristics.

Next in importance to the elongation of the body by full extension, is the position of the girdles. Since these connect the axial and appendicular skeleton, they have a mutually interacting effect. Thus the correction of postural adjustments frequently commences with an alteration in the inclination of the pelvis which is associated in turn with concomitant changes in the alignment of contiguous parts. Since stable standing demands the maintenance of the vertical projection of the center of weight within the confines of the safe middle third of the supporting base, no individual part of the whole can be moved significantly from the anatomical position without evoking com-

pensatory adjustments which affect the mutually interdependent alignment of all other parts.

The postural adjustments of the young, aged, weak, sick, and dejected differ obviously from those of the healthy and vigorous young adult. They have one thing in common, submission to the pull of gravitational stresses. In these individuals the equilibrating postural contraction of the antigravity muscles is insufficient to maintain the degree of extension characteristic of the young and the healthy. It has been assumed widely that the poor bodily mechanics incidental to such alignments, expressed as augmented rotatory moments, increase energy metabolism so profoundly as to be a primary source of fatigue. At this point there is confusion as to whether lack of muscle strength is responsible for the malalignment, or whether the latter induces degrees of exhaustion which make the maintenance of strong extension impossible.

One of the most distinguishing characteristics of postural contraction as compared with the phasic contraction of skeletal muscle, is the economy with which it may be maintained for prolonged periods of time without evidence of fatigue (2). No one has yet succeeded in demonstrating that poor bodily mechanics augment energy metabolism significantly (27, 30). Increased rotatory stresses secondary to the assumption of mechanically poor postures are equilibrated with ease. To correct such stances would require the strong phasic contraction of the antigravity extensors. Indeed, when "poor" postures are examined from a biologic rather than a mechanistic viewpoint, they appear to be compensatory. They are the stances requiring the least energy for their maintenance.

Two additional arguments have been used to condemn mechanically poor postural adjustments. Since they throw the weight of superimposed parts on structures not suited to maintain them, they may give rise to a type of microtrauma which may lead to pathological deviations from the normal which may be associated with pain. Thus the application of mechanical supports or devices aimed at a redistribution of weight, often relieve incapacitating discomfort. Many so-called poor postures are disfiguring without being the source of pain.

Many years ago Goldthwaite postulated an anatomico-mechanistic basis for chronic ills related to the visceral functions (14). The literature on this subject is voluminous and uncritical. The flat chest, abdominal visceroptosis, and crowding of the pelvic organs of the individual with poor posture are credited with a leading rôle in the pathogenesis of innumerable diseases. This concept is based upon more or less tenuous evidence (6, 25, 29, 34, 37, 47, 48), without regard for the wide margins of safety under which all organ systems function, and the paucity of proof that the anatomical position of a viscus is a valid criterion of the adequacy of its physiological behavior (1, 3, 16).

The rehabilitation of the postural adjustments of the sick and injured gives rise to several fundamental problems which have yet to be explored. Those secondary to traumatic lesions of the bony levers and their articulations are too individual for generalization. The orthopedic surgeon, the skilled craftsmen who construct orthopedic appliances, and the physical therapy technician form a team well equipped to handle these purely mechanical problems. How amenable postural adjustments are to correction in patients suffering from functional diseases or psychosomatic disturbances is unknown. Long hospitalization because of debilitating intoxications, infectious, deficiency, or metabolic diseases have a uniform effect on the postural adjustments. Inactivity is invariably associated with loss of strength and tone. The automatic compensatory adjustments by virtue of which the hydrostatic effect of gravity on the circulation is counteracted function so poorly that sudden transitions from prolonged recumbency to the vertical posture may end in syncope. The technique of graduated change from recumbency to standing is well known and needs no discussion. When there is partial or complete loss of function in large muscle masses, insufficient tonus may exist to prevent the pooling of blood in the splanchnic reservoir or the extremities. The application of an abdominal binder or of elastic bandages to the supporting appendages may then be of value. We have discussed the literature on gravity shock in detail elsewhere (19).

Little has been written on the physiology of motor learning. The re-education of semi-automatic postural adjustments in stance and locomotion when one or more of the appendages have been amputated is a fertile field for investigation. The reciprocal use of the limbs gives the adult amputee a life-time familiarity with symmetric kinesthetic patterns which are precipitously replaced by postural models defective in configuration. In addition these may be distorted by the persistence of phantom limb sensations (52). How gaps in proprioception affect the acquisition of motor skills dependent upon bilateral limb use is worthy of study, especially in relation to problems of vocational rehabilitation.

Lower motor neuron lesions give rise to two types of problems which indirectly affect postural adjustments: first, the preservation of denervated skeletal muscle if regeneration is likely to occur, and second, the re-education of intact motor units and muscle groups when there has been a falling out of aggregates of muscular tissue. If muscle

power is to be either preserved or increased, intelligent attention must be given the selection of optimum rates and duration of working. Every athlete knows that hypertrophy of muscle and increase in power result only from systematic repetition of bouts of work which exceed in severity those which can be performed easily. This is known as the overload principle (4, 45). Fear of fatigue renders ineffective otherwise rational therapeutic exercise programs. Fatigue is a reversible physiological phenomenon probably incapable of damage to muscle. The way in which postural exercises are administered suggests that when they result in stance improvement, this is due to the assumption of a more advantageous mechanical balance, rather than to increase in strength.

The technique of muscle re-education is a topic of current controversy (11, 23, 39). The individuation of desired skills from mass responses is the natural method of motor learning. The newer approach consists of the meticulous building of increasingly complex patterns of movement from the carefully learned primary actions of isolated muscles or small groups.

Poor posture was credited with responsibility for the breakdown of men under the stress of battle conditions during the last war (5, 9, 24, 35, 38, 46, 55). This gave rise to considerable attention to the problems of body mechanics. As a result posture training has been practiced extensively in the schools of this country during the interim between the last and the present war. Whether or not this has had a telling effect upon the bearing of our youth awaits full publication and study of the medical data of selective service boards.

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PHYSIOLOGICAL ASPECTS OF PHYSICAL THERAPY AND REHABILITATION

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Physical therapy always has participated in the rehabilitation of the sick and the disabled. At the present time it constitutes an integral part of practically all rehabilitation programs. Its importance in the treatment of wounded soldiers and veterans was fully appreciated by the medical profession during and following the last war. Marked advances were made in the treatment of wounds and injuries by the application of physical therapy principles. Many of these principles were employed in definitive therapeutics and were further utilized during the period of convalescence. The use of such principles contributed to the establishment of maximum physical and psychological benefits which, when combined with supplemental vocational or professional training, qualified the individual to resume his economic and social responsibilities as a citizen in civilian society. The earlier advances of physical therapy have been maintained somewhat since that time but probably not to the high degree of development obtained at the close of the last war. New interest and an even greater appreciation of these principles have de veloped during the current conflict. It seems very likely that noteworthy contributions will be forthcoming which will hasten and even exceed the maximum amount of rehabilitation obtainable a few years ago.

Physical therapy may be defined as "the use of various kinds of physical agents and physical therapeutic procedures, such as light, heat, water, electricity, massage, therapeutic exercise, and manipulation in the treatment of injuries and diseases." Even though physical therapy is one of the oldest branches of therapeutics, it has been only within recent years that serious efforts have been made to place it on a rational or scientific basis. Empirical usage has established a number of well recognized therapeutic procedures and many of these are utilized by practitioners of all kinds as well as by the laity. It is a rather sad commentary that the medical profession in general has been the last to fully accept physical agents as valuable therapeutic aids. Many members of the profession

ave been disinclined to take an active interest in he development of a thorough understanding of he use of physical agents. Had the same interest n physical agents been shown as there was in drugs nd related forms of medication, undoubtedly here would have developed in medical schools a ranch of science comparable to that of pharmaology for the study of the biological reactions of ormal and diseased tissues to physical agents, nd for the determination of dosage, tolerance, nd dangers of physical agents.

From what is known of the biological reactions f the body brought about by the action of physical gents, it may be said they are similar to those hich develop in response to drugs, namely, stimuation, depression, irritation and counterirritaion. Physical agents which increase the activity or unction of a tissue or an organ are said to stimuate; those which decrease the activity or function, epress; those which set up mild inflammatory rections, irritate; and those which produce homoloous reflex vascular changes in the deeper tissues re said to cause counterirritation. Physical gents, like drugs, set up physical and chemical eactions in tissues; the emphasis of the former is erhaps on physical reactions, and that of the latter on chemical reactions. Either or both types of herapeutic agents may give rise to local or general eactions.

With regard to the administration of the various ypes of therapy, drugs and physical agents alike ay be applied locally or generally. In the case of rugs, general administration is usually administered internally, either parenterally or orally, hereas in general applications of physical agents, hey are applied externally. One of the outstanding ifferences between the use of drugs and physical gents is that of dosage. With drugs it is possible o give any measured quantity of medication in he form of a gas, liquid or solid, but as a rule, such s not the case with physical agents. The units of easure of physical agents are not readily handled, nd it is impractical, therefore, to prescribe efinite quantities of such things as heat, cold, ght, or high frequency current. Dosage of physial agents, for the most part, is established on the asis of the individual's response. The conditions nder which physical agents are administered have een established largely by clinical usage. It is the esponse of the tissue or organ to the physical gent which is the desired result. The end result ay be the same as that sought by the use of a rug. The means of determining the reaction of the ody or parts of the body to physical agents are xactly the same as those utilized in the determiation of the responses to drugs. The physiological eactions are as easy to evaluate, and sometimes uch more so, than those brought about by drug herapy. In many instances the results of both types of therapy are identical, and when combined may reenforce the reaction of each other. Not only the same tissue responses may be established with physical modalities, but they may be obtained more quickly and may be controlled more satisfactorily. In either case when used in the treatment of diseased tissues, it is the utilization of the physiological responses which causes the functional restoration of the part to its former state of structure and function. Both kinds of treatment are used for the purpose of re-establishing healthy homeostasis of bodily functions.

From what has been said, it seems obvious that efforts should be made by medical scientists, medical practitioners and particularly by medical schools to establish either departments of biophysics or separate departments of research medicine comparable to pharmacology for the purpose of studying the different reactions of normal and abnormal tissues to physical agents. Clinical research should be conducted to appraise the more or less empirical methods which are currently employed in physical therapy. Efforts should be made to make the rationale of physical therapy parallel that of the scientific therapeutics now enjoyed by medicinal therapy. Fortunately, a number of prominent investigators and clinicians have become interested individually in this phase of therapeutics. They have contributed greatly to the knowledge of this subject. Many praiseworthy contributions have been made and physical therapy has gained wide recognition of its merits during the past few years. Its progress has brought about not only a better understanding of the fundamental principles which are employed in therapy, but also in diagnosis as well. Many diagnostic procedures based on purely physical principles have been developed and are utilized by various medical specialties. Other diagnostic procedures are employed more or less exclusively by physicians specializing in physical therapy. Both its progress and recognition have expanded so greatly that it is becoming recognized more and more as a specialty of medicine. There appears to be an active movement underway at the present time to consider physical therapy as a branch of specialized medicine and to change the name to "physical medicine." In due time this achievement no doubt will be realized.

THERAPEUTIC AGENTS. The common modalities utilized in physical therapy may be summarized as follows: (1) Heat (natural or artificial) supplied by the sun, carbon arcs, infrared generators, luminous heat lamps, hot packs, hot water bottles, electric pads, electric blankets, steam, hot water, exogenous heat of chemical reaction, diathermy, hot paraffin, poultices, hot compresses, mud, or various kinds of insulating material which serves to retain body heat. (2) Massage (superficial and

deep stroking, manual kneading or compression of soft tissues and frictional agitation of subcutaneous tissues). (3) Hydrotherapy (hot or cold baths, contrast baths, whirlpool baths, Hubbard tub treatments, paraffin baths, ablutions, showers, douches, packs, compresses, steam baths). (4) Therapeutic Exercise (passive, static or muscle setting, assistive, active assistive, active, active resistive, symmetrical and asymmetrical exercises, training in muscle coordination, posture training, muscle re-education, instruction and assistance in the use of various kinds of equipment provided by a medical gymnasium). The various kinds of exercise equipment ordinarily included are: pulley weights for the arms and legs, exercise mats and plinths, shoulder wheel, abduction ladder, rowing machine, stationary bicycle, Kanavel table, posture mirrors, walkers, parallel bars, stall bars, Sayre head sling, foot and ankle exercise apparatus consisting of different kinds of rockers, incline planes, circumduction tops, and inversion treads. (5) Ultraviolet light (provided by sunlight or supplied either by the carbon arc or by hot or cold quartz mercury vapor lamps). (6) Electric currents supplied by galvanic, faradic or sinusoidal generators. These currents may be employed either for diagnostic or therapeutic purposes. Galvanic currents used in electrophoresis are employed to introduce into the skin and subcutaneous tissues certain medicinal agents, such as histamine, mecholyl, epinephrine, nupercaine, copper, zinc, magnesium, sodium, iodide, or salicylate ions. Penetration of such agents is more rapid than that provided by topical application. This is especially true when it is desired to treat subcutaneous structures or deeply situated tissues of ulcerated areas. Diathermy (long and short wave) is used as a source of conversion heat. (7) Manipulative procedures combined with or associated with therapeutic exercise employ active or passive stretching of tendons or ligaments, realignment of joints, correction of abnormal stresses and strains exerted in various parts of the body by improving the body mechanics, recognition and treatment of functional imbalance of symmetrical muscles which have to do with stance or locomotion.

PHYSIOLOGICAL REACTIONS TO VARIOUS PHYSICAL AGENTS. In the presentation of the physiological reactions of the body or parts of the body brought about by application of physical reagents, only the generally accepted principles will be mentioned. It is not the purpose of this report to present controversial subjects or give the evidence for and against the different concepts. No effort will be made to thoroughly and completely document the statements made, nor to supply concrete quantitative data to support the conclusions contained in the publications which have been used as source material. An effort will be made to present in more or less outline form what is believed to be th generally accepted physiological principles whic have been established by various investigators.

Heat. Heat is a form of radiant energy which ma be absorbed by or radiated from the surface of th body by conduction, convection or radiation. Th portion of the electromagnetic spectrum usuall considered as heat energy ranges from the begin ning of visible light through the far infrare according to the following subdivisions: visibl light 3,900 to 7,600 ÅU, near infrared from 7,600 t 15,000 ÅU, intermediate infrared from 15,000 t 30,000 ÅU, and far infrared from 30,000 to 150,00 ÅU (1).

The human skin behaves almost as a perfec "black body radiator" (2, 3). It radiates nearly al infrared rays (97 per cent or more) or absorbs t the same extent all of the heat rays which fall upo it (4). The most effective heat energy insofar a penetration and physiological reactions are con cerned are those of the near infrared range. Th wave length of the infrared emitted by the skin a the usual temperature (34°C.) is 94,400 ÅU (3) Owing to the high water content of tissues, th heat capacity is very high, and likewise, because o the extensive vascularity of the tissues, heat ma be rapidly dissipated from a local area by means o the resultant increase in the flow of blood an lymph.

The local effects of the local application of hea may be summarized as follows (5, 6): With mild o moderate amounts of heat, there is a vasodilata tion of the peripheral blood vessels involvin arterioles, capillaries and veins; these change probably result from direct action of heat upon th blood vessels and reflex vasodilatation resultin from true autonomic reflex responses. There is a increase in the rate and volume of blood flow, a increase in the capillary pressure which increase the filtration pressure and accelerates the fluid los from the blood stream into the tissues, thus estab lishing a tendency to edema formation and a increase in the formation and the rate of lymp flow. Excessive heat actually leads to the produc tion of edema and is usually referred to as "hea edema." There is an increase in the permeability o the walls of the capillaries which permits varyin amounts of plasma proteins to escape into the tis sues. Numerous inactive capillaries open up an become markedly dilated. This vascular respons results in the establishment of an erythema of th skin and an elevation of skin temperature. Th resultant skin temperature is a temperature equi librium established by a number of factors: 1, in creased by heat absorbed from the exterior plus a increase of skin temperature as a result of vasodila tation, and 2, decreased by heat loss resulting fro radiation, evaporation and convection combine

with the dissipation of heat by the blood and lymph.

Associated with the elevation of skin temperature is an increase in the metabolism of the subcutaneous tissues. The local application of heat lowers the pH and increases the CO_2 and O_2 tension. When the blood is heated, the dissociation constants are altered in such a way that proteins combine with base of sodium and potassium bicarbonate, the CO_2 thus freed is added to the free carbonic acid originally present; the acidity is greatly increased (about 0.02 pH units per 1°C. or 1.8°F. rise), and the CO_2 tension is raised. The blood changes combined with the increased formation of acid metabolites resulting from increased metabolism causes a significant increase in the acidity of the tissues. Temperatures between 64.4°F. and 102.2°F. (7) cause the rate of O_2 exchange between the blood and the tissues to be increased, and the blood on entering the vein contains 50 to 65 per cent of its saturate value of oxygen. Above 102.2°F. the flow of blood through the capillaries becomes so rapid that the blood entering the vein simulates arterial blood and contains 91 per cent of its saturated value of oxygen. The vascular and perivascular changes that occur in the tissues as a result of severe heat (above 103°F.) bring about tissue reactions comparable to mild inflammation. Temperatures exceeding 115° F. augment these inflammatory reactions, and, if continued for sufficiently long periods of time, cause definite signs and symptoms which may be diagnosed as various degrees of burn.

Prolonged and repeated applications of radiant heat to the skin also produce pigmentary changes (8). The skin may become somewhat darker and take on a brown mottled appearance. The physical and chemical reactions of skeletal muscle are altered by local application of heat. The changes in muscle behavior as recognized clinically are those of relaxation, increase in muscle power and increase in muscle coordination.

The reactions to heat when applied locally are not confined to the local area. Reflex vasodilator changes occur in the skin of other areas of the body causing an increase in skin temperature. Varying amounts of secretory activity of the sweat glands may accompany the vascular changes. Some of these reflex responses may be brought about by segmental autonomic reflexes, and others by the action of the elevated temperature of the blood upon the heat regulating centers of the hypothalamus (preoptic and supraoptic regions) (9). Reactions of the blood vessels of the skin are associated usually with concomitant vasoconstrictor responses of the vessels of the splanchnic area. The local lowering of capillary pressure in the blood vessels of the intestines facilitates the absorption of water.

Other systemic effects may be noted as a result of local application of heat; the rate and depth of respiration may be increased, the heart may become accelerated, there may be an increase in cardiac output, the pulse may become stronger, and the pulse pressure may increase. Changes similar to those which develop with generalized hyperthermia become apparent if the local heating is continued for a long period of time.

General heat. Hyperthermia—artificial fever therapy. With general heating there is an elevation of body temperature, an increase in metabolism of 7 per cent with each degree F. elevation of temperature. The oxygen consumption may be increased 100 per cent or more with a rise of only 1°C. The heart rate may be accelerated from 100 to 150 per minute depending upon the individual's reaction to heat, the degree of elevation of body temperature, and to some extent the method of heat application. The cardiac output may be increased to as much as 400 per cent; the circulation time is reduced and the velocity of the blood stream markedly increased. The pulse volume and the total volume of blood flow to the extremities are increased. Other cardiac changes take place, such as shortening of the conduction time and alteration of the filling and emptying times of the ventricles (10).

Changes in the blood include a reduction of blood volume owing to the loss of fluid by excessive perspiration; the blood constituents become concentrated as a result of anhydremia; the blood becomes more alkaline because of the formation of an uncompensated alkalosis resulting from the partial acapnia established by pulmonary hyperventilation. The pH may be increased to as much as 7.9. Leukocytosis ranging from 10,000 to 60,000 per cubic mm. of blood usually develops, and there is evidence of increased hematopoiesis as shown by an increase in the number of young cells present in the circulating blood. Usually there occurs a relative increase in the neutrophils and a decrease in the lymphocytes following fever therapy. The average increase of the neutrophils according to Krusen (11) is 25 per cent and the lymphocytes decrease 23 per cent. There is a serious loss of blood chlorides which requires continued replacement in order to prevent the development of heat cramps. As a rule there are no significant changes of the nitrogenous constituents of the blood. The CO_2 tension of the blood may be reduced to 20 mm. or less. There is an increase in blood sugar, pulmonary ventilation may be increased from 5 to 6 liters per minute to 35 liters or more, and the RQ is elevated above one. A rise of body temperature decreases gastric motility, hunger contractions, gastric acidity and gastric secretion. There is also a decrease in the secretion of bile and pancreatic juice. The urine

and lymph become more alkaline; there is an increase in the amount of sodium bicarbonate in the urine. Immunity reactions, both local and general, are said to be accelerated. Prolonged continuation of an elevation of body temperature by general heating ultimately gives rise to symptoms of circulatory collapse.

Cold. Cold may be applied to the body either locally or generally in the form of water, ice, cold air chambers or cold packs. Varying degrees of local refrigeration may be accomplished by the application of carbon dioxide snow, liquid air, or other rapidly evaporating substances, such as ethyl chloride. To summarize the effect of local application of cold, there is a decrease in tissue temperature, a decrease in the rate of circulation, the volume flow of blood is diminished (cold reduces the circulation to such an extent that the tissue temperature may be very little above that of the surrounding temperature). During the local applications of cold, the low tissue temperature remains more or less localized without producing any significant general effects; however, reflex changes do occur in other parts of the body. Cooling of an extremity may cause similar vascular changes in the contralateral extremity and in the opposite extremities as well. The skin, subcutaneous tissue and mucous membranes may exhibit reflex vasomotor changes in widely separated areas of the body; pelvic and abdominal viscera, such as the bladder and intestines, may contract. The vascular responses are believed to be brought about by direct action of cold upon the blood vessels, by reflex vasoconstriction, and by chemical vasodilator substances, histamine-like or H-substances.

Exposure to temperatures below 64°F. produces secondary hyperemia. In such conditions there is an erythema of the skin brought about by an increase in the number of open capillaries, dilatation of arterioles and capillaries, and opening of arteriovenous anastomoses. There is an increase in the rate of blood flow through the vessels of the skin. Under such conditions the volume flow through the extremity as a whole may be reduced owing to the vasoconstriction of the vessels of the deeper tissues. The vascular reactions of the skin are said to be caused in part by axone reflexes and in part by chemical vasodilator substances.

Direct measurement of the penetration of cold into human gastrocnemius soleus muscles two inches beneath the surface by means of thermocouples showed the tissue temperatures to fall from 95° to 75° or 85°, usually to approximately 80° (12). The lowering of the temperature of the muscle was accomplished by placing an ice bag on the skin for 30 to 50 minutes. Reactive or secondary hyperemia may be absent under certain conditions: 1, generalized chilling of the body or rapid lowering of the body temperature so that contraction of the small arteries may become the dominant action; 2, when the localized chilling is quite rapid or when the cold penetrates the tissues deeply enough to cause constriction of the small arteries; and 3, when the sensory fibers in the arterioles have degenerated. Reactive responses to cold increase muscle tonus, causes shivering, increases the tightness of elastic tissues, causes leukocytosis, hyperglycemia and an increase in oxygen consumption of the tissues in regions of the body not depressed by the direct action of cold. Phagocytosis is depressed and immunity reactions are retarded. In the absence of adequate compensatory reactions, chilling the body lowers the leukocyte response, impairs phagocytosis, produces stasis and tissue anoxia.

General cold. General application of cold may be done by using either a cold room, special refrigeration machines, or ice packs. There results a fall in body temperature to 90°F. or lower; such low body temperatures may be maintained for days (13). Metabolism is markedly depressed, the pulse rate is slowed, cardiac output is diminished, blood pressure becomes reduced to such a low level that the pulse may not always be detected, the peripheral veins collapse, and the apex beat diminishes to such an extent that it cannot be felt. There is marked depression of the central nervous system, and other systems of the body become markedly hypofunctional.

Massage. The following physiological changes have been observed as a result of massage (14): 1, light stroking produces a transient dilatation of capillaries while heavier stroking brings about a more prolonged vasodilatation; 2, vigorous massage causes no significant change in the hydrogen ion concentration of the tissue, and little, if any, alteration of oxygen consumption; 3, the red blood count becomes increased, the response being more marked in the presence of anemia; 4, there is an increased oxygen capacity of the blood; 5, massage increases the removal of waste products from both normal and abnormal tissue. Exudates and extravasated blood resulting from injuries or fractures are absorbed at an accelerated rate; 6, it produces vasodilatation, muscle relaxation and sedation; 7, it also establishes a tendency toward drowsiness. This latter effect is especially true when the massage is light and rhythmical. It is obvious that the predominant effects of massage are on the nervous and peripheral vascular systems. The effects are those brought about by mechanical stimulation of the cutaneous and subcutaneous structures; they are both reflex and mechanical. Rhythmic application of mechanical energy to vascular structures provides an extravascular pumping action upon the vessels comparable to that caused by active contraction of skeletal muscles.

Hydrotherapy. The physiological effects of local application of hydrotherapeutic agents are princi-

pally those brought about by the application of heat, cold or mechanical stimulation. Some heat modalities, such as the whirlpool bath, combine the local effects of heat with those of the local effects of gentle mechanical stimulation. The two physical agents acting simultaneously reenforce one another in bringing about muscular relaxation; their soothing sedative effects usually cause a reduction of pain and discomfort. Contrast baths (alternate applications of heat and cold) cause a sequence of alternate stimulative and depressive changes in the cutaneous and subcutaneous tissues. Sprays and douches of various kinds provide a method of applying strong mechanical stimulation to the skin. Generalized contrast baths in the form of a Scotch douche may be employed to elicit bodily reactions produced by a combination of heat, cold, and vigorous mechanical stimulation. Varying degrees of generalized bodily changes consisting of tonic or sedative reactions may be obtained by the proper application of hot or cold water at specified hydraulic pressures.

The initial temporary reactions which result from the application of cold establish such phenomena as vasoconstriction of the peripheral vessels, pallor of the skin, shivering, increase in the respiratory and cardiovascular activities. These primary reactions are usually referred to as the "action," whereas the terminal secondary changes are referred to as the "reaction." The "reaction," therefore, results from the compensatory changes of the body in response to the primary cardiovascular and other reflex changes brought about by the so-called "action." The general effects upon the respiratory and circulatory system are similar to those brought about by the application of moderate cold (65°F.).

Therapeutic exercise. The exact mechanism of shortening of the contractile elements of skeletal muscle is still unknown. Extensive knowledge regarding many of the physical and chemical reactions responsible for the energy changes during muscular contraction and relaxation has been ascertained; to date, there has been very little practical application of this knowledge. Initiation of muscular contraction apparently begins either with the formation of a junctional potential or of a chemical transmitter, probably acetylcholine, at the myoneural junction; possibly a combined action of the two initiates muscular contraction. Clinical observations have shown that repeated contractions of loaded muscles (muscular contraction against resistance) increase the size, power and efficiency of contraction. Regular exercise creates a feeling of exhilaration and improves muscular coordination. Over-exertion leads to fatigue. As yet there appears not to be any objective physical or physiological sign which may be used to determine the optimum amount of exercise which will provide maximal physical benefit without causing fatigue. A suitable physical sign or test of some kind would be extremely useful in the treatment of paretic or paralyzed muscles.

The development of energy during severe muscular work has been determined to be from 10 to 14 calories per minute as compared to the basal level of one calorie per minute (15). Severe muscular exertion causes a liberation of energy amounting to one calorie per second. The stimulating effects of exercise on the respiratory, cardiovascular and cutaneous functions are well known. The investigations of Lindhard (16), Hill (17) and others have demonstrated a profound increase in the functional activity of these systems. For example, tests on human subjects showed that the oxygen consumption increased from 250 cc. per minute to 3,500 or 4,000 cc. per minute, and that the basal pulmonary ventilation increased from 4 to 6 liters per minute to 100 or more. The stroke volume, cardiac output per minute, and oxygen consumption of the heart were markedly increased even though little increase in the size of the heart occurred during strenuous exertion. Other tests showed that the maximum oxygen debt which the body is able to undergo is equivalent to somewhat more than 75 calories. Mechanical efficiency usually varies between 21 and 28 per cent. Training causes an increase in vital capacity of the lungs, and the range of pulmonary ventilation is increased.

Widespread usage of the "rest cure" for the treatment of tuberculosis, certain neuropsychiatric conditions, and for numerous orthopedic and neuromuscular abnormalities has been influential in obscuring the value of physiologic exercise. The indiscriminant use of prolonged bedrest, sometimes combined with rigid immobilization of different parts of the body, has led to numerous disorders which may be attributed directly to excessive inactivity of the tissues. A few of these abnormalities may be mentioned: Trophic disturbances of the skin, unstable vasomotor reactions of the extremities, weakened or abnormal cardiovascular regulation, disturbed functions of the gastrointestinal tract, muscle weakness, muscle wasting and incoordination, abnormalities of posture, limitation of motion of joints, diminution in the elasticity and extensibility of connective tissue, osteoporosis of the bones, and disturbances of the functional control of the sweat glands. Many of these undesirable reactions could be avoided in patients by the judicious usage of the proper kind and the proper amount of therapeutic exercise.

The importance of a specific program of physiologic activity is becoming realized more and more by those responsible for the management of surgical cases. The institution of specific programs of active exercise soon after operation has been found extremely useful in preventing postoperative com-

plications and in hastening postoperative recovery. Orthopedic, neurosurgical, an many other special or general surgery cases are required to resume an active exercise program within a day or two following operation. Therapeutic exercises and reconditioning activities have proven to be extremely useful therapeutic adjuncts in the postoperative care of many surgical patients.

Ultraviolet light. The portion of the electromagnetic spectrum designated as ultraviolet light exrends from 3,900 to 1,800 ÅU. It is subdivided into two parts, namely, near ultraviolet radiation from 3,900 to 2,900 ÅU and far ultraviolet radiation from 2,900 to 1,800 ÅU (18). The actinic rays of sunlight are limited to the near ultraviolet light. The important physiological and biological reactions may be outlined as follows (19): 1, antirachitic properties (wave lengths from 2,800 to 3,200 ÅU) are brought about by the activation of sterols and the formation of vitamin D; 2, erythema (wave lengths from 2,800 to 3,200 ÅU and 2,400 to 2,700 ÅU) results from photochemical actions within the skin which cause the formation of vasodilating substances, probably histamine-like or H-substances; these may cause intense redness and localized urticarial reactions. The inflammation of the skin appears as a dermatitis, and various degrees of burn may be recognized with symptoms ranging from a slight erythema to extensive vesication, desquamation, edema and pain; 3, pigmentation (wave lengths ranging from 3,800 to 3,000 ÅU) develops after a single intense irradiation or following repeated small exposures; 4, bacteriocidal effects—almost all bacteria are killed or attenuated when exposed to ultraviolet energy between the wave lengths of 2,000 and 3,000 ÅU. The wave lengths of maximum bacteriocidal efficiency lie between 2,400 and 2,700 ÅU. Inactivation of many viruses (tobacco mosaic, rabies, influenza, poliomyelitis), toxins (staphylococcus, diphtheria, tetanus), and bacteriophages takes place by exposure to ultraviolet wave lengths which are actively bacteriocidal.

Effects on blood cells. There is an increase in the number of erythrocytes, leukocytes, and thrombocytes, an increase in the hemoglobin content, a temporary rise in the reticulocyte count, a relative lymphocytosis and eosinophilia, and a decrease in coagulation time.

Effects on circulation. Blood pressure may be lowered, elevated or unchanged. Pathological hypertension is usually reduced. Cardiac output may be increased. Intense irradiation may cause cardiac acceleration, and the pulse usually becomes fuller and stronger.

Metabolic changes. Moderate irradiation increases endogenous nitrogen metabolism, diminishes residual nitrogen, increases the excretion of uric acid, increases the fat content of the blood, the blood cholesterol, blood calcium and phosphorus, decreases the blood sugar and temporarily increases the basal metabolic rate. Repeated irradiation may cause a 10 to 15 per cent reduction of the B.M.R. The RQ may be increased to unity.

General tonic effects of ultraviolet light (20) include the development of a feeling of exhilaration, improvement in appetite, improved function of the gastro-intestinal tract, increases mental alertness, and, as a rule, it has an analgesic effect on painful areas. Overdosage of ultraviolet light may reverse these beneficial tonic effects.

Acceleration of tissue repair. Wounds, indulent ulcers, healthy and infected granulation tissue, when stimulated or mildly irritated by ultraviolet light, usually heal more rapidly.

Sensitization. The photodynamic action of ultraviolet light reacting with certain drugs, dyes, and pigments brings about a hypersensitization of the skin to actinic rays. This reaction must be borne in mind when treating patients receiving sulfanilamide or related chemotherapy. Occasionally such patients develop severe photodynamic reactions.

Electric currents. The electromedical currents employed in physical therapy may be divided into four different groups. 1, Direct current (galvanic). 2, Low frequency currents (faradic, sinusoidal). 3, Static currents. 4, High frequency currents. In general, the physiological reactions brought about by these different kinds of currents fall into three main groups. (a) Electrochemical—which includes such phenomena as electrolysis, polarization, and electrotonus; (b) Electrokinetic phenomena—stimulation causing an increased functional activity of tissues, direct kinetic effects of the electrical currents, and indirect kinetic changes caused by muscular contractions; (c) Thermal reactions. Some of the physiological responses to these various currents may be summarized as follows: Direct current (galvanic) gives rise to the following electrochemical effects: 1, active hyperemia; 2, stimulation of sensory receptors producing a tingling sensation and a feeling of warmth; 3, increases acidity in the region of the positive pole, and alkalinity in the region of the negative pole; 4, changes in irritability associated with anelectrotonus at the positive pole and catelectrotonus at the negative pole; 5, slight thermal effects causing a small elevation of tissue temperature; 6, reduction of pain associated with mild irritation and counterirritation; 7, electrokinetic effects in the form of stimulation of nerves and muscles when changes in the intensity of the current occur.

Low frequency currents. Electrokinetic effects are caused by tissue stimulation and by indirect effects resulting from muscular contractions. 1, stimulation of sensory nerve endings causes tingling and moderate burning sensation; 2, moderate vas-

omotor changes (usually vasodilation); 3, indirect thermal changes caused by muscular contraction.

Static modalities. The predominant reactions are the electrokinetic effects, such as, 1, stimulation; 2, "intercellular massage" (resulting from mechanical energy supplied by the impact of the electrical currents); 3, increase flow of lymph; 4, increase in the drainage of inflammatory exudates; 5, sedative effect on pain receptors; 6, indirect kinetic effects resulting from muscular contractions.

High frequency currents. Diathermy is believed to cause only thermal effects. All physiological reactions, such as vasodilatation, muscle relaxation, increased perspiration, and sensation of warmth, result from the conversion of the high frequency currents into thermal energy.

Manipulation. By manipulation is meant the application of mechanical force to one or more parts of the body for the purpose of producing internal changes either in the microscopic structure of tissues or in the alteration of their respective position to one another. The force of manipulation may be supplied by the person himself or it may be applied from some external source. The physiological responses are those brought about by alterations in tissue tension associated with the readjustments of stresses and strains. Other changes may result from the elongation of tissues, such as increase in the extensibility or an alteration in the elasticity. Concomitant vasomotor reactions may develop with changes in the status of the fibrous connective tissue. There may be a reduction of pain because of the release of abnormal tension exerted upon the pain receptors; this is frequently associated with a reduction of reflex muscular rigidity which may likewise cause a diminution of pain. The procedures which are employed are those of active and passive stretching of abnormal muscles, tendons, ligaments and fibrous connective tissues. Correction of faulty alignment by means of improving the body mechanics relieves postural stresses. Reduction of dislocations or subluxations of joints either of the axial or appendicular skeleton may be employed when indicated.

Rest. The physiological reactions of rest are those of decreased functional activity of the involved tissues. Some of the common manifestations are muscle relaxation, decreased vascular supply, tissue temperature, secretory activity, receptor activity (causing adaptation and a reduction of pain if pain is present), and tissue metabolism. It is employed therapeutically, 1, to facilitate tissue repair; 2, to provide protection against internal and external mechanical forces; 3, to diminish tendency to edema formation; and 4, to aid in the reduction of joint effusion.

SOME OF THE THERAPEUTIC PRINCIPLES USED IN PHYSICAL THERAPY. The following is a brief summary of some of the therapeutic principles based upon physiological reactions of tissues to physical agents:

A. Reactions of heat, either moist or dry: 1, the vasomotor responses increase the circulation and nutrition of the tissues; 2, tissue metabolism is increased; 3, there is usually muscle relaxation; 4, reduction in muscle spasm; 5, there may be a diminution of swelling, although not infrequently, heat augments swelling especially if the part is dependent and there is some injury to the tissue. The undesirable effects of edema and swelling may be offset by employing elevation of the part, massage and active exercises.

B. The most beneficial reactions of massage are those of: 1, muscle relaxation; 2, vasomotor reactions which increase the nutrition and blood supply to the tissues; 3, increase in the venous and lymphatic drainage which combats vascular congestion and edema; 4, mechanical enery applied to combat fibrosis and the development of adhesions.

C. Therapeutic exercises are employed: 1, to reduce tissue swelling; 2, hasten tissue repair; 3, improve the tonus of skeletal muscle; 4, counteract the development of muscle weakness and muscle atrophy.

D. Ultraviolet light may be used for: 1, its antirachitic, metabolic, photochemical, and bacteriocidal properties; 2, it is beneficial in treatment of wounds and skin diseases; 3, it may be used as a tonic or as a general metabolic stimulant to increase bodily resistance to infections.

E. Preventive therapy utilizes active exercises to maintain maximal functional activity of the non-injured or non-diseased parts of the body.

F. Manipulative procedures are employed: 1, to overcome contractures; 2, to overcome limitations of joint motion resulting from adhesions or from functional or structural changes in the soft tissues surrounding joints; 3, to improve faulty alignment by means of the application of cervical traction or by manually correcting faulty malpositions of joints of the extremities, sacro-iliac or vertebral joints.

G. Rest: Limitation of motion of movable parts may be provided by means of compression bandages, splints, braces, elevation boards, or casts. This phase of treatment is usually provided by the orthopedic service.

Diathermy is employed as a form of heat. The thermal changes develop because of the formation of conversion heat in the deeper tissues of the body. This provides an excellent source of heat for the deeper tissues, such as muscles, tendons, bones; sub-acute and chronic inflammatory diseases of the deeper tissues, such as arthritis, cellulitis, chronic pelvic inflammatory diseases are successfully treated with this type of heat. Certain

acute infections, such as lymphangitis, lymphadenitis, furuncles and carbuncles usually respond quite satisfactorily to diathermy. Repair of bony tissue may be assisted in conditions where the regenerative powers of the bone are abnormal (delayed union, non-union).

Diagnostic procedures. The diagnostic procedures commonly employed are those of electrodiagnosis and of voluntary muscle testing. They are employed in the study of the central nervous system or peripheral neuromuscular system. Testing cutaneous sensibility is carried out in order to correlate the sensory disturbances of the skin with the alterations of motor function. The information supplied by such tests is useful particularly in the treatment of peripheral nerve injuries. Posture examinations are made, 1, to detect abnormalities of body mechanics; 2, to determine the presence or absence of abnormal tensions of soft tissues; 3, to locate the abnormal stresses which are exerted upon the ligaments, tendons, and joints; 4, to evaluate the relative power of the skeletal muscles of the body; 5, to ascertain the limitations of motion of the different joints of the body; 6, location and detection of muscle tenderness, soreness, rigidity, presence and distribution of referred pains also are included in the realm of diagnostic procedure in the field of physical medicine.

Current conception of the rôle of physical therapy in rehabilitation. It is believed that physical therapy can participate most effectively in rehabilitation by utilizing the following procedures: 1, institute physical therapy treatment as soon as possible; 2, treat the individual as a whole which means treating the psychological aspects of the patient's disabilities as well as the physiological and pathological processes; 3, in prescribing physical therapy treatments, make use of principles which are based on physiological reactions of the body, and outline a treatment program which is best suited to correct the individual and collective abnormalities of the person; 4, co-ordinate and integrate the physical therapy treatment program with other types of treatment. When the above mentioned procedures are followed, physical therapy will contribute maximum service to the rehabilitation of the individual.

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PHYSIOLOGICAL ASPECTS OF CONVALESCENCE AND REHABILITATION FOLLOWING CENTRAL NERVOUS SYSTEM INJURIES

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There is scarcely any type of organ injury in which rehabilitation of the disabled individual must be undertaken in so specific a way and with such close adjustment to the individual case as in brain injury. From the outset, the questions to be kept in the foreground are whether, and in what degree, the disturbances of performance can be reversed; what can be done to promote spontaneous restoration; and, if a full restitution is not to be expected, how we should proceed with retraining of the patient. Thus the problem as to the capacity of the brain for anatomic or functional restitution occupies the center of interest.

We are not at all well prepared to solve this problem. This may appear astonishing in view of the enormous body of facts that has been collected by physiologists and clinicians. The main reason for this lies, I think, in the concentration of interest on the problem of localization and the attempt to establish correlations between definite symptoms and definitely circumscribed areas in the cortex. The functional relationship between the two has been left to more or less speculative theory that did not include the function of the brain in its entirety.

Consideration of this factor immediately focuses attention on the dynamic nature of all performances and of symptoms insofar as they constitute an expression of the attempt of the organism to come to terms with an outerworld situation. Consequently it will be understood that before considering rehabilitation we must discuss the general problem of the origin of symptoms and of restitution in brain damage. The point of view assumed here has originated from observation of the behavior of a large number of patients with brain lesions and injuries of varied extensions and localization.

In my presentation I shall refer a great deal to my own experiences. I feel a little uneasy about it, but the limitation of space at my disposal does not permit me to refer to all of the literature; on the other hand, such a restriction is justified in view of the fact that this symposium is intended to present an informal discussion of the problem rather than a historical review of the data of the field.

A. *The origin and classification of symptoms in brain damage.* The symptoms we observe in damage of the central nervous system are not at all simply manifestations of changes in definite functions and structures. Analysis of the symptoms (11) causes us to distinguish between the following groups:

I. Symptoms which represent direct sequelae of impairment of the substratum and consist of defects of performance. These are the negative symptoms of Hughlings Jackson.

It was long believed that any performance might be lost or impaired, and this depended simply on where in the cortex a lesion was situated. In general this is true. A lesion of the posterior central convolution, produces sensory loss; a lesion of the anterior central convolution, disturbance of movements; a lesion of a particular part of the left third frontal convolution, language difficulties, etc. But this interconnection falls short if we consider the disturbances more carefully. In cases of lesion of a "sensory" or "motor" area, the relevant performances do not drop out uniformly. The lesion produces effects according to a characteristic selective process. The sequelae of a cerebral lesion rarely take the form of a complete loss of performance; more commonly the performance affected undergoes modification. This modification is a result of a systematic disintegration of the concerned function (Hughlings Jackson). Structurally, this disintegration invariably exhibits the same features, whatever region is involved, be it the spinal cord, the subcortical apparatus and regardless of whether reflexes, motility, speech, thinking, or feeling is concerned (cf. 6, p. 28). The typical form of this disintegration has been traced to a mass of diverse symptoms. Only through appreciation of this form can we understand the symptoms. It is necessary, therefore, to discuss it here, though only in the broader outlines, which may be formulated as follows:

1. All direct damage causes a rise of the threshold and retardation of excitation. The receptivity of the patient is reduced. It takes him much longer to react. This usual change manifests itself in the fact that patients may succeed perfectly in a task when given sufficiently long exposures, but fail in the same task with brief exposures, i.e., when examined by the tachistoscope. Thus the tachistoscope becomes an important instrument for revealing impairment (cf. 7, p. 99).

Prolongation of time of stimulation does not always bring about improvement of performance. The patient may perceive if the stimulus is strong enough but after a certain time he may cease to see the object in spite of continued stimulation. Later the object may appear again. It seems that the

threshold changes during stimulation. This abnormal alteration of the threshold through stimulation concerns—depending on the part of the cortex damaged—different performance fields. For instance, in lesions of the occipital lobe the whole visual field or the homonymous half fields may be affected, in diffuse damage of the brain all performances more or less. Ineffectiveness of stimulation appears earlier in a part of the performance field which normally has a higher threshold. Here even the first stimulation, if it is not very strong, may not be reacted to while the parts with normally lower threshold reactions may be fairly normal. A consequence of that is constriction of the visual field especially of its temporal periphery where normally the threshold is higher than in the center. Such constriction is observed in diffuse damage of the occipital lobes or in lesion of the frontal lobes; in the latter case it is due to impairment of "higher" mental function. Stimulation of one part of a performance field may influence the performance in other parts of the same field. One effect of this is the so-called Ringscotomata (cf. 7, p. 54). Another one is the following phenomenon observed in hemiamblyopia. An object presented in the hemiamblyopic half field may be observed even though somewhat blurred, but if concomitantly another object is presented in the healthy half field that object presented in the impaired half field may disappear and come back if stimulation of the healthy field is discontinued (cf. recent confirmation of such previous observations in the publication of Bender and Furlow). Excitation of a damaged field requires an abnormal amount of energy (cf. 6, p. 59). Stimulation of the periphery may not bring about any useful perception and therefore dislocation of excitation to a better functioning part occurs (dislocation phenomenon). Under this condition sometimes double vision is observed, if the patient experiences a clear dislocated picture but at the same time retains a—mostly unclear—perception from the excitation of the stimulated part (monocular double vision) (cf. 6, p. 50).

2. If excitation takes place despite the obstacles, it spreads abnormally and lasts an abnormally long time. This again is due to the disturbance of the process of equalization by every damage. For example, the patient may be unable to locate the precise point stimulated on his skin. On the other hand, there is a long after-sensation. Examples here are the phenomena of tonic innervation, a repetition of the same movements, reiteration in reflexes (clonus), etc. A word grasped by an aphasic with great difficulty sticks and influences subsequent performances, perseverates. (Concerning the origin of perseveration and ways to avoid it.

3. A further characteristic effect of the damage is that performances of the organism are determined to a much greater extent than normally by external factors (cf. 6, p. 154). As a result of loss of structure, patients are deprived of former experiences; thus external stimuli acquire an abnormal importance.

4. Modification of the patient's performance results predominantly from a blurring of the sharp boundaries between "figure" and "ground" (cf. 6, p. 109, 151). In any function of the organism the excitation in the nervous system is distributed in such a way that the process in a circumscribed area differs as to form and intensity from the state prevailing in the rest of the nervous system. To the process in the circumscribed area there corresponds that which we call performance designated by the term "figure", to the process in the rest of the nervous system the term "background" or, more briefly, "ground," applies. When we look at any picture we at once see and understand what is figure and what is background. The terms figure and ground can be applied not only to visual but to all performances.

Habitually we ignore the background of a performance and pay attention only to the figure. But figure and background are intimately interconnected. Neither can be properly evaluated without the other. All damage in the nervous system, especially in the brain cortex, disturbs the relation between figure and ground. The sharp differentiation of figure from background suffers, figure and background intermingle, inducing a general leveling. This is sometimes carried to the point of inversion, where the figure becomes background and the background figure. Many symptoms become understandable from this point of view.

5. Defects found in special examinations do not always reveal conclusively the real disturbances in everyday performances. The behavior of the patient with hemianopsia is a case in point. It is known that even a complete hemianopsia does not necessarily disturb the patient a great deal in everyday life. The patient may realize his defect only as a general diminution of his vision in one eye. Examinations have shown that the reason for this is that the patient does not have a "half field" of vision in his everyday experiences. The hemianopic defect exists only in perimetric investigation, not in everyday vision. For an explanation of these phenomena which are of particular interest from the theoretical as well as the practical point of view, I would like to refer to 6, p. 53 and 131.

II. Symptoms due to separation of an undamaged area from a damaged one. By such separation, or as I call it "isolation," the function of the undamaged area is modified in a definite way (cf. 6, p. 132, et seq.). Here we are dealing with the positive symptoms of Jackson. It is reasonable to

assume that in the normal nervous system all parts function in interrelation with the whole, or at least with more extensive fields. Performances in a given field are therefore also determined by the functioning in other fields. Loss of certain performances, through damage of their substrata, brings about the modification of other depending performances. Innumerable examples could be adduced from pathology—the appearance of exaggerated or abnormal reflexes, such as Babinski's sign, in lesions of the pyramidal tract, in the field of speech logorrhoe in sensory aphasia, lack of control due to the motor cortex, etc.

III. A third group of symptoms is due to the effect which the pathological process in the damaged area exerts on other parts of the nervous system, for instance by irritation of the immediate neighborhood. We call these depending symptoms (cf. 14, p. 198). One other instance is the missing of a performance due to a disturbing effect of one part of an apparatus on the rest of the apparatus. If the other part is not in gross anatomical connection with the first, the origin of the functional defect may not be immediately apparent. In some cases where both frontal convolutions represent one apparatus, damage of the area of the one side may produce a defect of motor speech. If the damage consists of a scar, excision of the latter may bring the other undamaged side again into function, at least to a certain degree. In such a case the patient may improve after operation of a scar or a tumor even with respect to the symptoms which we believe are in relation to the affected area. In fact, the existence of such a mechanism can be assumed only if it is proved that the part secondarily disturbed is an essential part of the whole apparatus. Only then can we expect an improvement by operation. However, we cannot expect this if the symptoms are due to isolation. It is evident that this distinction between secondary symptoms and symptoms due to isolation has a definite bearing on therapy.

IV. The fourth group of symptoms are expressions of the tendency of the organism to avoid catastrophic conditions (cf. 6, p. 35 et seq.). In order to understand this some introductory remarks are necessary here.

If patients with severe brain injuries are observed without prejudice, one will frequently find considerable variation in performance. Apparently similar tasks will sometimes be properly performed, sometimes not. Incapacitation seems to be an aftereffect of a preceding failure. This becomes understandable when we do not simply note and record the fact that the organism is unable to perform but that the patient is changed in his total behavior. He looks definitely dazed, changes color, becomes agitated, starts to fumble, his pulse becomes irregular, his is sullen, evasive, exhibits temper, or even becomes aggressive. Subjectively he feels more or less disturbed and afraid. In the situation of success on the other hand he is steady, interested, cooperative and feels much more at ease. We call the state of the patient in this situation of success "ordered condition," and in the situation of failure "catastrophic condition." It is important to know that the patient in the catastrophic condition is not only incapable of performing the required task which exceeds his impaired capacity but fails consequently also in performances which he is able to carry out in the ordered state. This aftereffect explains the variations of performances mentioned before.

The sick organism has a strong urge to meet all demands as well as possible; its existence is bound up with such an endeavor even to a greater degree than in the case of the healthy organism. Only in this way can he avoid catastrophies. That is particularly significant for the sick organism, because only then can he exploit his preserved capacities.

There are different ways in which the organism evades the threat of catastrophe. One of these is self-exclusion from the world, i.e., loss of consciousness. In some cases that may occur even in seemingly unimportant situations. It is to be observed, for instance, if the individual has to solve a simple problem in arithmetic and cannot do it, or if he is demonstrated to somebody or if he is afraid of the examiner, etc. (One has always to be aware of this possibility in the procedure of retraining.)

Other more suitable means of avoiding catastrophe are the following: The patient seeks tranquility, avoids company. He tries to avoid anything unexpected. The mere fact that the stimulus comes from a situation not belonging to the present milieu is irritating, because the patient has to shift and may not be able to do that. The patient seeks to surround himself with a protective fence that will prevent impinging stimuli from entering. He may build such a fence by everlastingly doing something. Concentration upon a particular activity makes him relatively impervious to the undesired and dreaded stimulation from outside. When he is confronted with a task he cannot cope with he will stick to the performances he is able to fulfill. Thus he appears abnormally fixated and rigid.

A particularly interesting and important phenomenon resulting from this tendency to avoid catastrophies is excessive orderliness. Everything in the patient's environment must have a definite place. Behind this formal geometry there is quite a utilitarian motive, namely bringing each object within the patient's reach with a minimum of effort on his part. He gets excited if somebody changes the arrangement.

Because of these protective devices the patients often (cf. 6, p. 38) are utterly unaware of their

deviation from the normal and of their own state prior to injury. They may have compensated in their attitude and behavior in such a way that the defect causes no difficulty at the moment. A patient who had been shot through the chiasma opticum was at first totally blind. As long as this lasted he was unaware of being blind. He used to talk of visual things like any seeing person; he was quiet, his behavior was orderly, and one could see that he managed to get along without difficulty in the hospital environment. Later his injury improved and he regained sight to a certain degree. Now he became upset: he sought to orient himself by means of sight, but failed, owing to its imperfection. He was thus less well adapted to his world than he had been when blind. Now, for the first time, he spoke of something not being right with his vision, and this previously reasonably contented man dropped into a state of depression. "What's to become of me if I can't see?" he would cry.

Adaptation with loss of awareness of the defect occurs without the patient's being conscious of it. The following is an example of this: A patient of mine suffering from visual agnosia could not recognize a single letter visually. Yet he could make out the meaning of words, by way of kinesthetic experiences gained through tracing the seen lines with movements of his head. The modification of behavior which helps to avoid catastrophic conditions finds its most salient expression in persons having major defects.

In severe lesions of one side of the cerebellum, we may find a "tonus pull" of the body toward the diseased side (cf. 11). All stimuli which are applied to this side (stimulation of the vestibulum, the skin, the eye) are met with greater intensity in comparison to the effect of stimulation of the healthy side. This abnormal "turning toward the stimulus" (cf. 6, p. 118) leads to abnormal deviation in walking, falling, *past-pointing* all toward the diseased side. Usually these patients display, if not stimulated, an abnormality of posture in the form of tilting of the body, especially of the head. Subjective as well as objective disturbances immediately appear (falling to that side, etc.) as soon as the patient resumes the "normal" position of the body. Apparently the abnormal posture represents an adjustment of the organism to the defect (the abnormal pull towards the one, *e.g.* left side) and a new state of order which guarantees normal functioning. The organism is able to utilize more effectively its remaining capacities. This compensation is brought about in one type of case by tilting of the body toward the diseased, in another toward the healthy side. (Poetzl, Goldstein.) We can state the facts by saying: in the first case the organism found a new order by yielding to the tonus pull, while in the second it checked the effect of the tonus pull by producing a pull in the opposite direction. (cf. 17.)

B. *The procedure of rehabilitation in relation to the various forms of symptoms.* The discussion of the origin of deviations from the normal in a defect of the brain has revealed that a definite abnormality is not at all simply a direct consequence of the latter but an expression of the struggle of the particular individual with his defect and his attempt to perform as well as possible the tasks arising from the environment. This aspect must determine the direction of our procedure in retraining and rehabilitation.

Before we begin with retraining we want to know to what degree spontaneous restitution has occurred or can be expected to occur. Our discussion of the origin of symptoms will make us cautious in our judgment about this point. Restoration of a performance may be the effect of a new organization by adjustment to the defect which in itself is not improved at all. This is of the utmost significance for the question of localization. Such a pseudo-restitution by adjustment does not allow us to assume that another part of the brain has taken over a function to which it was not related before.

As to retraining we shall be inclined to follow the ways in which the organism spontaneously brings about improvement of performances by adjustment to the defect and to help the individual to enforce the natural procedure. This is often the correct way to improve a particular performance. But it will not always bring about the best result in rehabilitation. Spontaneous improvement of some performances by adjustment with the help of protective mechanisms may allow the use of a capacity only under certain conditions. That may incapacitate the man in work which he is able to fulfill but cannot because this condition contradicts the work. Then a better result will be reached if we teach the man to renounce some of these protections and induce him to use his remaining capacities even if sometimes catastrophic conditions may occur. We must help him to face the danger, to bear some disagreeable occurrences and protect him by other means against severe catastrophies. Here the confidence in the teacher or other persons who supervise him is of paramount significance. It is very important that the patient discover that the danger in using his capacities is not as great as he feared. We shall often have to decide how much of his incapacitation he must bear and how much he may compensate. Our decision will be determined by the kind and severity of the defect, the personality of the patient, the situation in which he has to live and to work, what kind of work he will be able to fulfill in spite of his impairment, etc. When direct improvement is to

be excluded we shall teach use of compensatory means. Here systematic building up of roundabout ways is the procedure of choice.

The deviations from the normal which have to be considered in rehabilitation are of two kinds:

Those which concern the *general performance capacity*, physical as well as mental;

Those which concern *special performances*, such as mental capacities, motility, speech, reading, etc.

Deviations of the first type occur particularly in diffuse damage of the cortex or in lesions affecting the frontal lobes or the posterior pole of the brain. Circumscribed defects correspond to localized lesions in the one or the other area.

1. *Rehabilitation in impairment of the general performance capacity.* Evaluation of the patient's complaints may give some insight as to his general capacity to work. But for a definite decision about what he may be able to do in real work and for what kind of labor he would be best suited, more precise facts are needed. One can gain them by the application of two types of exact methods. One may select some physical or mental tasks, observe the individual's performance at them over a certain time and draw conclusions from the records as to his capacity for performances in general and in specific vocations. Because the tasks in these tests differ essentially from those the individual is accustomed to do, they are called "abstract performance tests." On the other hand one may observe the individual during actual labor and record his effectiveness during a certain time. This is a "concrete labor test" (cf. 7, p. 137).

The essential difference between the two methods consists in the following: The abstract tests reveal something about the course of the psychophysical processes in an individual in general, his timing, his promptness, regularity, irregularity, fatigability, etc., while the concrete tests give more insight in the capacity in a special kind of work. From the practical point of view it is much easier to use the abstract performance tests. This will be useful only if we are able to make conclusions from the results gained from them on the expected capacity for work. Comparison of the results taken from the same patient with both methods has shown this is possible.

The following very simple methods are appropriate in abstract testing: *a*, the reaction time test; *b*, the Kraepelin method of continual addition, and *c*, testing of motor capacity by ergographs. In the simple reaction test the patient has to press a key as quickly as possible on the appearance of a light; in the choice reaction test he has to react to a large light, not to a small one, etc. The times and errors are recorded in a series of stimulations. From the reaction test we obtain data for determining the average reaction time and, more important for our purpose, insight into the behavior during continuous activity from the curve corresponding to the time needed for carrying out the successive reactions. We learn something about the individual's endurance, capacity to learn, his fatigability, and his ability to make a choice. In the addition test the task consists of adding pairs of numbers in a presented series of numbers as quickly as possible and to continue in this way for about ½–1 hour. The results of the number of additions in each subsequent minute are checked. They are then recorded as to errors and number of additions made in one minute. The number of answers is plotted with the number of minutes and combined in a curve, which allows insight in about the same directions as the reaction test.

Ergographic tests are particularly suited for study of fatigue and working capacity in the use of muscles. One can study the motor activity and power of one finger by a finger ergograph or of one hand by a dynamometer, or of the whole body by a large ergograph where the subject has to draw upward a handle attached to springs. The higher the handle is lifted the more springs are tensed, the greater the energy that the patient must use to lift it. There is certainly no small difficulty in getting a correct judgment about a man's capacity from the thus resulting curves but I can say from experience that the curves gained with these ergographs can be used very well for practical purposes in patients with brain injuries. The curves of the patients obtained with all the mentioned tests show characteristic deviations from the normal. It is impossible to evaluate these deviations by comparison with the curves of the particular individual in the healthy condition but they may be compared with the curves of average normals. The deviations from the normal curves are so definite that they can be recognized as pathological.

It is impossible to go into the details of the results gained with all these tests. Some may be reported as examples. In the reaction time test, for instance, the brain injured individual may differ from the normal by an increase of the reaction time, particularly by the occurrence of extreme fluctuations between bad and good performances and the sudden break of the curve. These abnormalities especially occur or increase on days when the patient does not feel well. Furthermore, all abnormalities are much more pronounced in the curves of choice reaction. Abnormalities in the addition test present themselves in deviations as to the number of additions solved per minute (height of curve), the capacity for continuous effort (length of curve), and the form of curve.

The results gained from the three ergographic tests may be summarized as follows: There are some patients with brain injuries whose scores in all three tests are almost normal. The mentioned

single characteristics can in no way be considered as definite indications of equal damage to the general capacities of the brain. It depends somewhat upon the localization whether abnormalities in these tests show or not. For instance, patients with lesions in the motor area rarely show such severe disturbances of the general capacities as those with lesions of the frontal lobes or particularly in the occipital lobe. The finger ergograph, where the activity does not need much strength, is particularly suited to give an insight in the "manner of work." This also was brought out by the fact that the results of this test correlate with the curves gained from the reaction test and the addition test. Comparison of the results of the tests may show differences and conformities. The following practical conclusions may be drawn up:

Patients with normal curves in these tests will not show any essential deviation from the normal in regard to either the manner of working or their strength.

Patients who present good results at the start but are forced to give up almost immediately are patients with impairment of motor capacities. However, similar results may appear in patients without definite circumscribed defect of motor activity. Abnormalities from the very beginning may be an expression of a difficulty in general working capacity. If a patient shows good results in the finger ergograph, but shows bad results on the other one, it indicates that he is physically incapacitated, but has good ability to concentrate, to attend and endure.

For organization of the "concrete labor tests" the following rules should be observed: The psychological conditions under which the man is working must be regulated as nearly as possible to conform with those of regular labor. The labor must have market value; the work must be continuous, and must be in the nature of piece work; the man should try his best but over-exertion should be avoided; concomitant medical control should prevent over-exertion. Each man's work should be controlled in all details as to the number of hours he works each day. Duration of interruption must be recorded. Curves of the capacity and wages of each man should be plotted. If the wages of the man remain below a certain average for a certain period of time, new investigation of the case should be made. It has been shown that it is not necessary to have the man work in real factories which makes the whole procedure very difficult; it is satisfactory for our purposes to use simpler workshops (cf. 7, p. 137).

If one compares the results obtained by the abstract tests with those gained in the workshop, they show a high degree of conformity. The following examples may illustrate this: A man with a frontal lobe lesion who is easily tired showed in the simple reaction test no abnormality as to time but great fluctuation in the choice reaction test. His capacity for addition was limited; he was quickly fatigued in the finger ergograph test and still more so with the large ergograph. From these findings we could conclude that his working capacity would be poor and fluctuating. This was confirmed by his record in the workshop over a period of 15 weeks. His wages were very low. He had to interrupt work often. This behavior was particularly striking as the man was very willing and skillful and did not give the impression of being sick.

Another case is a man with an occipital lobe lesion, visual agnosia, marked vasomotor disturbances, no paralysis; he works well and is willing to work. His curve of simple reaction was relatively normal. The reaction times were short, increased only after a long period and then not very much. In choice reaction he showed great fluctuation varying from day to day. His addition curve showed no essential deviation from the average number of additions, an average length of time and no great fluctuation. The ergograph curves were short showing an early decline and fatigability. One had the impression that the man tried his best, was not poor in any performance, but had early fatigue and fluctuations of capacity at one day much more than at another. His record in the workshop was similar. He earned quite a bit of money but his work fluctuated; on the whole he was able to do average work for a week. However, suddenly he may become so exhausted that he can no longer work. Two days later he may begin again and does very well for two weeks, but he again breaks down.

These two examples may show that it is possible to gain some judgment about the working capacity of the patient from the results with the abstract performance tests. Indeed, we are still at the beginning and our results are not at all satisfactory. But the principle seems to be sound and therefore recommendable. Research in this direction seems to me particularly promising for progress in theoretical as well as practical aspects.

Fatigue and perseveration. Fatigability and perseveration are often mentioned as obstacles in retraining and rehabilitation of brain-injured individuals. However, we find that in one and the same patient these phenomena do not invariably appear under all conditions. If we want to avoid these obstacles we should know which conditions particularly facilitate their occurrence and under which others they are less likely to appear. Consideration of the facts from this point of view is also of great interest for theoretical clarification.

Fatigue usually is considered due to increasing consumption of energy by work. Fatigue or fatigability is measured in terms of increasing impairment in continuous performance. Observation of

our patients shows that fatigue is not a simple function of the duration of continuous performance but depends to a high degree upon whether the performance in question is within or somewhat above the capacity level of the individual (cf. also investigations of Howard Bartley, 9).

The paradoxical situation may occur that fatigue may even decrease as the activity is continued, if for instance a later demanded task is "easy" to perform while the first task could be executed only with difficulty. A second point is that fatigue does not express itself simply as a slowing down of performance, but, at least at the beginning, in fluctuations of performance. Subjectively the individual feels not only incapacitation but also discomfort, uncertainty and distress. The phenomena occurring in fatigue show great similarity with those to be observed in the catastrophic condition and seem to be closely related to it. Our patients fatigue so easily because many normal tasks represent for them difficult tasks and produce distress. While fatigue in difficult tasks may thus be understandable, we may ask whether the same point of view is suited to explain also the occurrence of fatigue in continuous work *which qua task* is within the limits of the individual's capacity. I think it is. Continuation means a consumption of energy which deteriorates the function of the substratum changing so that a task which was previously easy to perform now is a difficult one. Thus mere continuation may produce catastrophe and fatigue. That becomes evident when in continuation of one and the same task fatigue sets in earlier than when the task is varied. Boredom and interest show their influence. That has to be considered particularly in testing situations. If, after we recognize the onset of fatigue, we change the task, the patient may perform better subjectively and objectively, particularly if the succeeding task is within the capacities of the individual, and especially if changing does not demand voluntary shifting on the part of the individual, a particularly difficult problem for many brain injured patients.

Performances which do not ask for voluntary adjustment and shifting are easier for these patients. Such "automatized" performances may be continued for a long time without the patient showing and experiencing fatigue. However, we frequently observe severe breakdowns after excellent performances. This suggests that the "symptoms" of fatigue are not signs of catastrophe but indications of imminent catastrophe warnings which, thoroughly considered may help prevent the latter. Patients with a mental defect manifested in lack of planning and foresight are particularly vulnerable. They do not recognize the protective danger signs of fatigue as such and become abnormally fatigued, particularly if they are made to continue work.

Perseveration is a frequent phenomenon in brain damage. I am inclined to assume that it is a secondary phenomenon due to incapacitation in some performances and a means to avoid catastrophe occurring under such conditions. As a matter of fact perseveration occurs particularly if the patient is forced to fulfill tasks he is unable to cope with. A patient, for instance, who has difficulty in arithmetic may be able to answer promptly as long as he has to solve problems which are within his capacity. The moment he is given a problem which he is unable to fulfill, he may either be thrown into a catastrophic state and not react at all or he may repeat the last correct result, or a part of it, in answer, i.e., he perseverates. However, if he is then given an example which he is able to solve he may again answer correctly and all perseveration disappears.

When we observe that the same patient under some conditions shows perseveration, under others distractibility, it becomes evident that we are not dealing with a primary defect of "rigidity." The sick organism tries to react to the task set before him as well as possible. Confronted with tasks which he can fulfill, he reacts successfully. If he cannot do so, he tries to react to that part of the task on which he is able to succeed by means of his remaining capacity, and he sticks to that rigidly, because thus he can best avoid catastrophe. But under certain conditions he becomes aware that he has not fulfilled the task correctly. Then he gives up the first reaction, I think because continuing it does not help in overcoming the distress. He tries again and may become attached to another part of the situation to which he is able to react, but again may feel that he is not performing the task demanded. Thus he appears abnormally distractible (cf. 6, p. 154).

Neither rigidity, perseveration or distractibility are defects *per se* but phenomena coming to the fore under various conditions that can be defined. They can be avoided—at least to a certain degree—by the same means by which abnormal fatigue can be avoided, understandable because ultimately they originate from the same cause.

2. *Rehabilitation in impairment of special performances.* We have no space to discuss here all the special defects observed in brain injuries in relation to retraining and rehabilitation. There is from the beginning the question as to how we should proceed with retraining. Should we simply help the patient to regain his lost performance capacity, to use it in the same way as he did before injury, or should we help him to learn to compensate with other performances? Our choice will depend primarily upon the degree of damage of the nervous and physical mechanism which is related to the performance in question.

I think it is correct to assume that to each

mental performance there corresponds a particularly constructed substratum in the brain, that functions in a definite way. The nervous mechanisms are, so to speak, predisposed. They develop during the growth of the individual and gain a particular organization by experience. They extend from the peripheral sense organs to the substrata of the most complicated mental performances. If such a substratum is damaged in its functioning, the organization as a whole may be maintained, the mechanism losing only some of these functions acquired by training. In such cases it may be possible and appropriate to retrain this functional mechanism by the same means by which it was built up in childhood. Hence it may be possible to acquire again the lost performances. This happens also in spontaneous recovery, where the apparatus is retrained by the demands of the environment.

If, after a thorough analysis of the symptoms, one is convinced that the brain matter is damaged to such a degree that some former functions are irreversibly lost, it will be necessary to proceed in another way. We shall have to help the patient to build up compensatory procedures in the same performance field. Even this, of course, will be impossible if the damage concerns an apparatus of so primitive a function as qualitative sense perception. In damage of a sense organ, it would be futile to try to build up a new sense apparatus by stimulation of the sense organ. This applies also to some higher central apparatus such as the apparatus which is the anatomic counterpart of recognition, i.e., in cases with visual agnosia or corresponding disturbances in other fields. If in these cases the apparatus is severely damaged, we have no other choice than to build up substitutes which may be performances of a totally different kind. That may be illustrated by a particularly characteristic example: The treatment of disturbances in word finding. There is one group of patients where the difficulty in finding words is mainly an expression of a personality change, an expression of impairment of "abstract attitude," which we shall discuss later. This change cannot be repaired if there is no restitution of the anatomical damage. The patient never regains the capacity of abstraction or if he does, only to a limited degree (16). For a person who is incapable of the abstract attitude, it is very difficult or even impossible to build associations that do not represent a connection he can experience concretely. They are in a situation similar to that of a person learning vocabularies of a foreign language that he does not understand. But their difficulty is still greater because, as a result of their impairment in abstract attitude, they cannot bring themselves, as can the normal individual, into that unnatural attitude which learning of such associations demands. There is no other means of helping the patient than by teaching him to find words in a roundabout way. Observation of the manner in which the patients themselves overcome their defect may be used as a guiding principle.

Frequently a patient, unable to find a name for an object or a person or an action, recites a little verse or quotation that he knows is related to the object and contains the word he cannot find. After repeating the verse, he immediately recognizes the word as that he has been seeking. It is characteristic that recognition of the spoken word is never disturbed in these patients.

A patient may sometimes be unable to evoke a specific word, but may be able to recite a series of words containing it. It is easier for the patient to learn a series of words belonging to a situation (for instance, the names of a group of objects that are in a natural relationship) than to learn separately words for individual objects. For example, he knows that "shirt," "trousers," "coat," "waistcoat," "necktie," etc., belong together. He learns these words as a series. If he requires one of these he recites the series and picks out the correct one. This process of learning can be facilitated if he gets to the point where one or more of the words occur to him spontaneously. Sometimes it helps to let the patient learn the words of a series in a definite rhythm, one that is familiar to him. Another practical method is to learn meaningful sentences which contain the required words. The sentences used in this way should depict concrete situations; the more concrete the situation is to the patient, the easier it is for him to hold it in mind and to find the word in this indirect way. There is another roundabout method. The object which the patient is supposed to name may remind him of a situation in which this object has important context, and out of this concrete situation the word may come to his mind. He may not, for instance, recall the name of a street, but he remembers that the street has the same name as the first name of a friend. This recollection immediately brings the name to mind in connection with other characteristics of this friend.

There is further possibility of improving word finding by use of visualization .The patient associates an object with the seen word. If he is able to retain it, he will later find the name by reading the visualized word. Sometimes it is sufficient for the patient to retain the visual picture of the first letter; this may be sufficient to produce the word. One can also utilize an association of the written word with an object. Then the patient will write the word if he sees the object; he will read the word and so will be able to speak it.

There are other types of patients with difficulty of finding words. They are not impaired in their abstract capacity; their difficulty in finding word

is due to disturbance of memory, especially in the sphere of language, or to disorganization of the so-called inner speech. In these cases a direct procedure of retraining is indicated in contrast to the indirect way. Improvement can be reached by rote learning or in the second type of cases by consolidating the structure of the words (cf. 7, p. 161). It is interesting to note that the difficulty in finding words diminishes with improvement of the inner speech without any special retraining of word finding itself.

I have mentioned retraining of the defect in finding words to emphasize the two basically different ways of retraining; the one consisting of direct re-education of an impaired capacity, the other consisting of building up roundabout ways.

3. *Rehabilitation of patients with impairment of the capacity of abstraction.* Usually the mental changes of patients with brain injury are considered from the point of view of impairment of special performances such as vision, speech, motility, sensation, etc., and of several functions such as attention, interest, emotion, memory, etc. Certainly, consideration of the behavior in all these respects is important for retraining and rehabilitation. However, that is not sufficient. Often the defect does not consist simply of diminution of one or several of the above-mentioned functions. The patient has undergone a change of his entire personality which modifies in varying degrees all these functions in a particular way. In all fields some performances are impaired or lost while others seem relatively well preserved. The symptomatological picture may seem very inconsistent. Therefore it is extremely important to know the structure of the mental impairment of the patient.

The normal individual displays two kinds of attitudes towards the world, which we call the concrete one, and the abstract one. In the concrete one we are given over passively and bound to the immediate experience of the very things or situations in their uniqueness. Our thinking and acting are determined by the immediate claims made by the particular aspect of the object or situation. For instance, we act concretely when we enter a room in darkness and push the button for light. If, however, we desist from pushing the button, reflecting that by pushing the button we might awaken someone asleep in the room, then we are acting abstractly. We transcend the immediately given specific aspect of sense impressions, we detach ourselves from the latter and consider the situation from a conceptual point of view and react accordingly. The abstract attitude corresponds approximately to what Henry Head has called—in relation to speech—symbolic behavior.

The healthy individual is able to shift voluntarily from one to the other according to the demands of the situation. Some tasks can be performed only by virtue of the one, others of the other attitude. During activity the concrete attitude is dominant, but if the course of action is interfered with or disrupted, abstraction is required to correct such disturbances and to continue properly the activity in question. Examination of a great number of patients with brain disease or injury has shown that certain types of brain pathology impair to a greater or lesser degree the capacity of abstraction (13). The patient is reduced to a more concrete level of behavior.

Patients with impairment of abstract attitude may not appear to deviate grossly from normals in everyday behavior, because many routine tasks do not require the abstract attitude once these tasks have been learned. However, on observation of the patient in a variety of situations it becomes evident that he does not react like a normal individual; he appears more stereotyped and reserved. He seems to lack initiative and spontaneity. Tasks which demand choice or shifting particularly reveal the defect.

From analysis of the behavior of a great number of such patients in various everyday and test situations we have compiled a long list of conditions at which they fail or which produce great difficulty for them. In general these conditions involve choice, comparison, planning, symbolism, detachment, etc.

Often it has been said that the defect of the patients consists of an inability to cope with new situations but that they are able to proceed in an abstract way as far as old experiences are concerned. As a matter of fact the patients fail equally in familiar situations as in new ones if they demand the abstract attitude. On the other hand they can successfully cope with new tasks though only as long as they do not require the abstract attitude. This is very important. If the defect would consist of an incapacity to handle new situations, the patients never would be able to learn anything and all our attempts to retrain them would be futile. On the other hand the patients are more likely to fail in new situations than in old ones because the former frequently demand new sets, that is, the abstract attitude.

A few examples taken from observation may illustrate the failures of the patients. A patient may be able to count if the examiner begins the series, "starts him off," but he cannot begin himself. Once interrupted, he cannot continue. He has to begin again at the beginning. He cannot stop at an arbitrary point upon demand but continues until definitely interfered with. He is unable to shift from reciting one series (e.g., numbers) to another series (e.g., days of the week), though he can recite each by itself. He can follow and even take part in a conversation on a familiar topic or the immediate situation, but if the conversation

shifts to another topic equally familiar to the patient, he cannot follow and is completely at a loss.

He may react successfully in a simple reaction test but he cannot react differentially to two lights. He may be able to read a word and at other times to spell it, but when asked first to read and immediately afterwards to spell it he cannot do it. He may succeed in throwing a ball into boxes placed nearer or further away, without being able to tell which box is farther or which one nearer. He may be able to orient himself in a complicated building which has become familiar to him but cannot say anything about even the simplest relations of rooms or floors to each other. He has greatest difficulty in pretending. He fails on performances which are meaningful only with relation to future expectations or occurrences.

The patient's speech in general may not be impaired; in certain situations he may have a great number of relevant words at his disposal. He will fail on the other hand, whenever the situation demands his conscious attention to the meaning of a word. The words have lost their meaning as symbols. They fit only in definite situations. The patient is particularly unable to understand that the same word could have different meanings in different situations. The patient may understand the word as part of a definite situation, but not if the word is used in another condition. Overlooking these language defects is likely to lead to the assumption mentioned above that the patient uses abstraction with regard to old material. As retraining is dependent to such a large degree on language, it is of greatest significance to take into consideration changes of language due to the impairment of abstraction.

If the patient with impairment of abstract attitude acquires certain materials by rote-learning, these new acquisitions lack stability. Only repeated experience of the usefulness of these connections in concrete situations will stabilize them. But such experience will often be missing. Here another important factor enters which tends to facilitate learning and consolidate the material acquired: the patient's confidence in the teacher. This confidence is a tremendous aid in the preservation of material learned meaninglessly and without insight.

Most of the examples I have mentioned concern the behavior of the patient with regard to school material. However, the same difficulties can be demonstrated in practical activities, handicraft and labor. If one has occasion to observe patients at such work, to see how they learn a new occupation, the significance of their defect for all procedures of rehabilitation becomes evident. If it is possible to organize the work in a way that the patient can grasp it concretely and handle the situation in a concrete manner, he may learn almost any type of work and accomplish good results. Wherever that is impossible it is in vain to tell him or to show him how to proceed. There are good possibilities for successful work even for brain-injured patients with severe damage, in such occupations as carpentry, book binding, shoe repairing, office work, etc., even in using machines in plants. Working on machines has been simplified so much at the present time that it presupposes very little abstraction. But only if taught in the right way will the patient be successful. It is particularly important that conditions be arranged in such a way that the patient's activity is interrupted as little as possible and that in such cases he is able to begin again without much deliberation. Furthermore, his work needs more control by others than the work of normal individuals, as he is more easily shocked by outside interference, by difficulties with defects of the machine, and may be unable to overcome such shock. The co-operation of the physician with experts in the various fields of occupation is here of greatest advantage (cf. 7, p. 208).

Not all patients with brain injury have impairment of abstraction. Whether it is present or not depends on the localization and severity of the injury. It is particularly prominent in frontal lobe lesions, even when the lesion is relatively small and circumscribed (13), but it can occur also in other localizations.

The patient does not recover from this defect if the damage of the brain is not restituted. Sometimes removal of scar tissue is beneficial in this respect (cf. 14, p. 198). There is no possibility for substitution of this function by the more or less intact remainder of the brain.

Lost abstract attitude cannot be regained by retraining (cf. 16, p. 53). The patient may learn to handle a task by means of a number of concrete procedures. He may achieve effectively correct results but never will he be able to fulfill the task in the normal abstract way. Sometimes, under the influence of training, success even in tasks which need abstraction may be attained. I do not deny that remnants of impaired attitude may in this way be set again in function. However, from observation and analysis of a great number of patients I am inclined to assume that such improvement as is found is mostly the effect of progressively better utilization of concrete reactions and not an expression of returned abstract attitude. That does not make such improvements less important. They are the basis of success in rehabilitation. However, they will be accomplished only if in all procedures one takes carefully into consideration the patient's impairment in his capacity of abstraction. If he is impaired in this capacity he has to be treated in an essentially different way than if that is not the case. Therefore examination of this mental capac-

ity has to precede any other procedures. Special tests which we have constructed for this purpose have proved to be very useful in the examination of impairment of abstract attitude (15, 16, 18, 19, 20).

SUMMARY. This presentation of the subject of rehabilitation following brain injuries is not at all complete. Limitations of space necessitated selection among the great number of problems that the observable facts offer for discussion. Under these circumstances, I deemed it expedient to take into consideration particularly such problems as may be of special interest for the physiologist, and for the rest to concentrate on general problems and to present these in such a way that application of the results to individual cases would afford a guide to appropriate treatment—whatever the special defect that the patient may show.

Of course this can be expected only if it is assumed that all disintegration of function in damage of the brain cortex follows essentially the same lines, and that reorganization can be accomplished in about the same way in every instance, irrespective of the location of the lesion and the special performance field affected. This is indeed the assumption that underlies all my explanations. It stems from the holistic approach that has proved so fruitful in understanding organismic life in health and disease (6). This approach has developed especially from my study of the sequelae of brain injuries and has stood the test of the years through the success it has brought in treatment of patients with such defects.

There is scarcely any material in pathology that lends itself so immediately to this theoretic approach as observation of cases with damage of the brain. A great number of symptoms—described in the literature, but hitherto only insufficiently interpreted—became understandable in this perspective and new facts revealed themselves over and over again. Insofar as this point of view considers pathologic phenomena merely variations of normal events modified according to definite rules, physiology may well profit from such an attitude in the analysis of symptoms in brain damage and in the rehabilitation of performances.

Indeed, my presentation is an endeavor not so much to make direct contribution by actual discussion of individual problems, but rather to offer such stimulation as the evidence of the usefulness of the methodologic approach in analysis of brain defects and in therapeutic procedure may provide. This is all that a short presentation touching on such comprehesive material can claim to accomplish.

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THE RÔLE OF THE AUTONOMIC NERVOUS SYSTEM IN PROBLEMS OF REHABILITATION[1]

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Autonomic nerves which modify either the function or the blood supply of the organs play an important part in the restoration of function in disease. This statement is supported by certain physiological experiments. It is well known that loss of blood is ill tolerated after the elimination of the buffer nerves whereby pressor reflexes are abolished. The loss of 20% of the blood was found to cause a more severe fall in blood pressure in dogs in which the receptors of the sino-aortic area had been removed than was observed in normal dogs which had been deprived of 60% of their calculated blood volume (Gellhorn and Pollack—29). The increased sympathetic discharges following a fall in intrasinusal pressure tend to maintain the blood pressure and thereby the circulation of brain and heart when the posture is changed in the human from the horizontal to the vertical position. Operative elimination of carotid sinus receptors leads to postural hypotension in man (2). In cases of orthostatic hypotension these reflexes are apparently not absent since the pulse rate increases on standing (Hallock and Evans—29), but apparently the sympathetic effects on the blood vessels are inadequte to maintain the blood pressure in the erect posture. It is of clinical importance that anoxia greatly weakens the carotid sinus reflexes (16). This makes it understandable that a degree of anoxia which causes no appreciable change in blood pressure in the reclining position leads to an abrupt fall and a collapse in the erect posture (8). Carbon dioxide, which offsets the effect of anoxia on the central nervous system, intensifies the pressor reflexes originating in the sino-aortic area (Vercauteren, Gellhorn and Pollack—29).

The regulation of the blood depots of the spleen (Barcroft, Scheunert, Izquierdo, Cannon; Grindlay, Herrick, and Mann—29) and liver (Grab, Janssen, and Rein—29) is accomplished through sympathetic nerve fibers and through adrenalin. The rôle of the liver under conditions of circulatory collapse has been emphasized by Rein (25).

The prevention of pathological states is also aided by modification of autonomic reflexes and increased sensitivity of autonomic centers. Dill (4) made the interesting observation that on repeated exposure to heat a given weight loss produced by sweating is brought about by progressively decreasing rises of body temperature. Apparently the autonomic centers which regulate sweat secretion in response to an elevation of the temperature of the body become increasingly sensitive under these conditions and prevent thereby the ill effects of overheating. Moreover, qualitative changes are observed in the chemical composition of the reflexly secreted sweat. The sweat becomes increasingly poorer in chlorides; an excessive salt loss is thereby prevented and the danger of heat cramps is averted or delayed.

These examples may suffice to illustrate the fact that in a number of conditions involving changes in the external or internal environment of the organism, autonomic reflexes are called forth which tend to keep the internal environment constant. Cannon (29) emphasizes the emergency functions of the sympathetico-adrenal system and illustrates them by the demonstration of the relative sensitivity of sympathectomized animals to exercise, hemorrhage, anoxia, cold, and hypoglycemia.

The importance of these mechanisms under pathological conditions similar to those studied in physiological experiments is obvious. It should be emphasized, however, that autonomic reflexes may, under certain conditions, act in an opposite manner and actually aggravate the severity of the disease process. Freeman and collaborators (29) observed that bleeding may lead more easily to circulatory shock in normal than in sympathectomized animals. The experiments suggest that sympathetic excitation following hemorrhage, although very important for the restitution of homeostasis, may lead to shock when persisting for long periods of time. The harmful effect of prolonged excitation of sympathetic nerves is apparently due to tissue anoxia which follows marked vasoconstriction. It leads to a reduction in the circulatory blood volume, which tends to aggravate the fall of blood pressure by impairing the venous return to the heart. The fall in blood pressure calls forth increasing sympathetic discharges via the carotid sinus, and thus a vicious cycle is established.

Another example of the fact that excessive sympathetic discharges may cause pathological processes is illustrated by Cushing's (3) experience that hypothalamic injury may cause peptic ulcer. It is assumed that hemorrhagic erosions of the gastric mucosa may develop as a result of emotional strains. The rôle of parasympathetic and sympathetic discharges in these conditions has

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been emphasized by Keller and collaborators (17, 18).

The examples cited so far illustrate two facts; first, that autonomic reflexes may play an important rôle in the recovery from disease; secondly, that excessive discharges may give rise to pathological changes in the organism. These data are of importance for medicine in war as well as in peace. Of still greater significance for problems of war medicine is the fact that thousands of men are repeatedly exposed to conditions of great emotional strain. It is of considerable interest that the effect of these emotional tensions in war is aggravated, not only by repeated exposure to conditions causing emotional excitation, but also by the fact that these conditions may arise at times when the autonomic centers are affected by cold or heat, anoxia or hemorrhage.

The recognition of the importance of the autonomic nervous system for problems of war medicine and rehabilitation depends on the understanding of the rôle of the autonomic centers for the behavior of the normal organism, and on the knowledge of their vulnerability under conditions which may be encountered by our armed forces during actual combat or during operations indirectly linked up with the war. The following paragraphs are an attempt to give a physiological basis for such an inquiry.

Emotional excitation, such as can be observed in animals, is linked up with the hypothalamus. The rage complex is elicited in cats on electrical stimulation of the hypothalamus (Karplus and Kreidl, Ranson—29); conversely, bilateral hypothalamic lesions, particularly in the mammillary bodies are accompanied by a diminished emotional response, cataleptic symptoms and somnolence (Ingram, Barris, Ranson, and Harrison—29). Release of hypothalamic centers from cortical inhibition leads to a facilitation of pseudo-affective response (sham rage) in animals in which both hemispheres had been removed. If the posterior part of the hypothalamus is destroyed sham rage can no longer be elicited (Bard—29). The rage response involves both somatic (extrapyramidal) and autonomic nervous systems. The participation of the latter is indicated by symptoms such as inhibition of peristalsis, piloerection, sweating, increase in pulse rate, blood pressure, and number of blood corpuscles (contraction of spleen), retraction of the nictitating membrane, and pupillary dilatation. Although sympathetic effects are frequently dominant, parasympathetic discharges play an important rôle, as seen by the occurrence of urination and defecation in man and animals under conditions of emotional strain. Yerkes (29 mentions vomiting as characteristic for emotion in chimpanzees, and Clark, Hunt and Hunt (29) observed, on firing a revolver, erection of the penis and defecation in infants and chimpanzees in addition to a series of characteristic motor discharges. Wolf and Wolff (28) present data suggesting parasympathetic as well as sympathetic effects on the stomach in man during emotional excitement.

Anoxia, which is of importance for our discussion because of its occurrence in high altitude flying, leads likewise to autonomic discharges. Stimulation of hypothalamus and medulla in anoxia and under control conditions, gives evidence of increased excitability of sympathetic centers in anoxia, since the rise in blood pressure and the contraction of the nictitating membrane is increased in response to a standard stimulus. The increased excitability of these centers in anoxia seems to depend on impulses originating in the chemoreceptors (9). Parasympathetic discharges are likewise enhanced under anoxia, particularly when severe degrees of anoxia or asphyxia are employed (cf. Gellhorn, pp. 152—29).

That cold and heat affect the hypothalamus has been clearly shown by Ranson and collaborators (23) and many others. Heat loss is regulated by the anterior hypothalamic area. Heat conservation is effected through the posterior hypothalamus. Cholinergic, although not exclusively parasympathetic, discharges are primarily involved in the regulation of heat loss whereas adrenergic mechanisms are called into action on exposure to cold. Autonomic and somatic discharges are integrated in emotional excitement as well as under conditions of stimulation of autonomic centers by heat and cold.

Excitation of autonomic centers results not only in nervous impulses which send excitatory and inhibitory impulses to striated muscles, smooth muscles, and glands of external secretion, but it affects likewise some glands of internal secretion. Increased secretion of adrenalin due to excitation of sympathetic centers occurs under conditions of emotional excitement, cold, hypoglycemia, and as a result of electrical stimulation of hypothalamic centers. It is recognized by its effect on denervated structures (heart, nictitating membrane, etc.), a hyperglycemic effect which is absent in adrenodemedullated animals, and by the biological assay of the blood of the adrenal vein.

The parasympathetic system likewise regulates hormonal activity under conditions leading to excitation of autonomic centers. Emotional excitement, anoxia, exposure to heat and cold, as well as direct hypothalamic stimulation with electrical currents lead to an increased insulin secretion which is regulated by the vagus (Gellhorn, Cortell, Feldman and Allen—29). This is shown by the fall in blood sugar in adrenodemedullated animals which have been exposed to these conditions. The hypoglycemic effect depends on the integrity of the vagus; no changes in blood sugar are observed in

adrenodemedullated-vagotomized animals, in which a nervous regulation of the activity of the adrenal-medulla and of the islets of Langerhans is no longer possible. In normal animals the effects of the sympathetico-adrenal system predominate over those of the vago-insulin system as far as the blood sugar is concerned. This seems also to apply to the human, but in pathological disturbances this balance seems to be altered. Excitement causes schizophrenic patients to liberate sufficient quantities of insulin into the blood so that its injection in hypophysectomized-adrenodemedullated rats which are highly sensitive to insulin, produces coma or hypoglycemic convulsions, whereas such reactions are not observed on injection of blood obtained from non-psychotic excited individuals (12).

The relation of the autonomic centers to other glands of internal secretion is less clear. However, there are sufficient data to warrant the conclusion that hypothalamic-hypophyseal discharges occur. It has been observed that the rate of secretion of the gonadotropic hormones is increased during sexual excitement (Westman and Jacobsohn; Brooks—29), but no conclusive evidence is available to indicate that this effect is present in other forms of emotional strain. Anoxia is known to cause an increased secretion of adreno-cortical hormones, (5) but the possible dependence of this effect on hypothalamic-hypophyseal discharges has not been studied as yet. Uotila (29) presents data suggesting increased secretion of the thyrotropic hormone on exposure to cold which was absent after sectioning of the hypophyseal stalk. This observation makes it probable that the rate of secretion of the thyrotropic hormone may likewise be regulated by the hypothalamus, but confirmatory evidence is needed.

The hypothesis that the rate of secretion of hormones of the posterior pituitary may be altered by hypothalamic impulses is suggested by observations of Rydin and Verney (26). These authors observed an inhibition of urinary secretion under the influence of emotional stress (fright or pain). The effect occurred in spite of denervation of the kidneys and adrenals and removal of the abdominal sympathetic chains. Moreover, it could be matched by injection of posterior pituitary extracts, but not by the injection of adrenalin.

From this brief and incomplete discussion it may be concluded that emotional strain and other conditions acting on autonomic centers in the diencephalon and medulla exert a profound influence on the whole endocrine system by altering the rate of secretion of the adrenalin, insulin, and at least some pituitary hormones. It appears probable that permanent or semi-permanent changes in the balance of autonomic centers, and thereby in the endocrine system, may be the result of frequent disturbances of these structures under conditions of stress and strain. It has been suggested elsewhere that the autonomic balance in psychotic individuals is altered, and that their changed behavior is definitely linked up with this central autonomic imbalance. This prompts the question as to whether repeated emotional strain or other stimuli acting on autonomic centers may cause chronic alterations in these centers. The experimental basis of this problem and its clinical and therapeutic evaluation will be discussed in the following paragraphs.

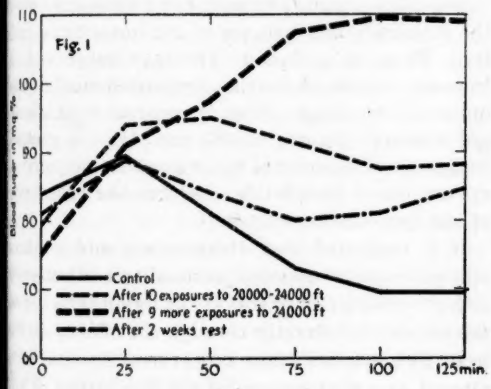
It has been shown by Gellhorn in collaboration with Cortell, Feldman (10), and Kessler (13), that rats subjected to electrically induced convulsions (electroshock) and to anoxia, react with an excitation of the centers of the sympathetico-adrenal and vago-insulin systems. It was also demonstrated by Page (22) that repeated electroshocks lead to an altered behavior of rats. On the basis of this experience it was decided to subject several groups of rats repeatedly to anoxia and electroshock respectively, and to study their autonomic balance and behavior under these conditions[2].

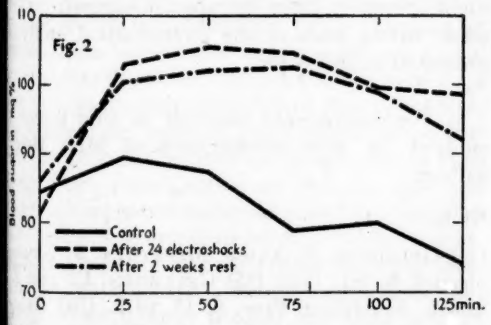
Exposure to anoxia was chosen as a test of reactivity of the autonomic centers. Since anoxia causes a rise in blood sugar of normal rats, a fall in blood sugar of adrenodemedullated animals, and no change in adrenodemedullated-vagotomized rats, it seems safe to conclude that hyperglycemia evoked under these conditions is a measure of the excitability of the sympathetico-adrenal system whereas fall in blood sugar is an indicator of the excitability of the vago-insulin system. If rats are subjected to a moderate anoxia for two hours they show a hyperglycemia; if, however, rats are subjected to five 25 minute periods of anoxia, a hyperglycemic phase is followed by a period of hypoglycemia (27). These experiments suggest that at first the sympathetico-adrenal system, and later the vago-insulin system predominates. This procedure adopted in our experiments as a test for the excitability of the sympathetic centers and the central autonomic balance was used in order to determine the effect of repeated anoxia and of repeated electrically induced convulsions on the autonomic balance.

Figure 1 shows that the blood sugar curve obtained from 13 rats followed the type described by Britton and collaborators. The rats were exposed to a barometric pressure of 280 mm. Hg for 5 periods of 25 minutes each, and after each period a blood sample was taken. The first sample obtained after 25 minutes of anoxia shows a slight rise in blood sugar whereas the last three samples show a

[2] As to the technique, the reader is referred to papers of Feldman, Cortell, Gellhorn and Kessler (29).

fall in blood sugar below the control level. The rats were then exposed 7 times during 9 days to a simulated altitude of 20,000 feet for 4 hours, and to an altitude of 24,000 feet for four hours during each of the three following days. Then the anoxia test was repeated with the result that the analysis of the blood revealed a greater initial hyperglycemia than under control conditions. Moreover, the blood sugar values remained higher throughout the experiment suggesting that the effect on the sympathetico-adrenal system had been increased sufficiently to obliterate the fall in blood sugar caused by discharges over the vago-insulin system during the latter part of the experiment. There-





after the rats were subjected to a second period of anoxia consisting of 9 exposures of 24,000 feet for 4 hours in 10 days. Then the blood sugar test was repeated and revealed now a considerable shift in the blood sugar curve. The hyperglycemic effect was greatly increased and progressed during the five anoxic test periods. The rats were then allowed to rest for a period of two weeks. Repetition of the test after this time showed that the initial hyperglycemia was similar in magnitude to that seen in the first control experiment. However, the hypoglycemic effect at the end of the test was still absent.

Experiments involving repeated application of electroshock showed similar changes (fig. 2). Prior to these procedures the rats reacted to anoxia with a typical biphasic blood sugar curve as described above. After the rats had been subjected to 24 electrically induced convulsions in 47 days the anoxia test was repeated and showed a greatly increased hyperglycemic reaction persisting through all 25 minute periods of the test. A period of two weeks was inadequate to restore the blood sugar response to the normal level but earlier experiments performed in collaboration with Arnett (29) showed complete reversibility after an interval of several weeks.

The experiments demonstrate that repeated anoxia as well as repeated electroshock lead to chronic changes in the activity of the autonomic centers as shown by the blood sugar curve obtained in anoxia. The reactivity of the sympathetico-adrenal system is greatly increased and extended in time so that the effect on the vago-insulin system is obscured. A period of rest is adequate to restore these reactions to normal. Repeated electroshocks cause the animals to become highly excitable (checked by 4 independent observers).

Fear-like reactions as described by Page (22) were seen in the present series whereas in earlier experiments the altered excitability of the rats appeared in the form of aggressiveness toward the experimenter or toward other rats in the same cage. The increased excitability of these animals led to an almost continuous defecation and urination during sampling of blood in contradistinction to the behavior of these animals prior to the administration of electroshocks. The fact that behavior changes were absent in the "repeated anoxia" group may be due to cortical damage.

The experiments show that conditions such as anoxia and electroshock, which lead to massive discharges from the autonomic centers exert, when applied repeatedly, chronic effects on these centers which are only slowly reversible. These chronic effects are characterized by a change in the balance of autonomic centers leading to an increased predominance of the sympathetico-adrenal system. This conclusion is based not only on the experiments reported in this paper but also on the fact that adrenodemedullated rats show either no or only slight changes in the reactivity of the vago-insulin system under these conditions (unpublished data). It is suggested that the changes in the reactivity of the autonomic centers may be linked up with alterations in behavior as seen in the animals subjected to repeated electroshock. This assumption is based on the following data:

1. Experimental and clinical observations indicate that hypothalamic disorders are accompanied by changes in personality.

2. Destruction of the hypothalamus eliminates cortical potentials (Obrador, Kennard—29).

3. Rats with extensive hypothalamic lesions

cannot be conditioned (Gellhorn, unpublished data).

4. Various procedures known to increase the excitability of the centers of the sympathetico-adrenal system (electroshock, anoxia, metrazol convulsions and hypoglycemic coma) profoundly alter conditioned reactions. (Gellhorn in collaboration with Kessler (13), Minatoya (14) and Seese (15).)

The experiments reported in this paper in conjunction with various experimental and clinical facts suggest that men, subjected repeatedly to conditions which cause an excitation of the autonomic centers in the hypothalamus and possibly the medulla, show a greatly increased responsiveness of sympathetic centers, which in turn may alter their behavior. The hypothalamic influence may be both direct and indirect; the former involving pathways from the mammillary body to the anterior thalamus via the Vicq d' Azyr bundle, and from there to the gyrus cinguli and other cortical areas (Papez—29), the latter due to the altered rate of secretion of one or more hormones. At the present time the increased rate of adrenalin secretion is of importance because adrenalin may cause either excitatory (Domm and Gellhorn—29) or inhibitory effects (Darrow and Gellhorn—29) on the central nervous system, and particularly on autonomic centers. The type of effect depends on the intensity and duration of the increased secretion. It is of interest to call attention to the observation of Kraines and Sherman (20) that injection of adrenalin may evoke neurotic symptoms. On the basis of these discussions it seems to be not unlikely that behavior disturbances due to repeated exposure to conditions of several of these factors are due to an imbalance of the autonomic centers in the hypothalamus and their direct and indirect influence on the cortex. From the physiological point of view two therapeutic procedures suggest themselves: first, to suppress hyperexcitability of sympathetic hypothalamic centers by means of drugs such as barbiturates whose effect on the hypothalamus is well established (21); second, to eliminate the effect of excessive adrenalin secretion by ergotoxin.

Summary. Procedures simulating conditions frequently encountered by our armed forces such as emotional excitement, cold and anoxia lead to an excitation of autonomic centers and cause discharges over the sympathetico-adrenal and the vago-insulin systems, and to an alteration in the rate of secretion of some pituitary hormones.

Repeated exposure to such conditions may alter the reactivity and balance of the autonomic centers. Thus, it is found that rats subjected to frequent periods of anoxia or repeated electrically induced convulsions, show in response to a standard stimulus (anoxia at 280 mm. Hg.) a greatly exaggerated response of the sympathetico-adrenal system which completely obscures the reactivity of the vago-insulin system.

It is suggested that these autonomic changes may profoundly influence personality and behavior either by the direct effects of the hypothalamus on the cortex or indirectly through the effects on the brain by hormones whose rate of secretion has been altered as a consequence of the excitation of autonomic centers. Some therapeutic suggestions are made on the basis of the physiological analysis presented in this paper.

In the experiments reported in this paper I enjoyed the able collaboration of Miss Helen Safford.

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PSYCHOSOMATIC APPROACH TO PHYSIOLOGICAL DYSFUNCTION AND DISEASE

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I. *Psychosomatic concepts in relation to recent advances in physiology.* The term psychosomatic had an aura of newness and strangeness to most physicians a decade ago. Those interested in research have become familiar with it and have found it increasingly essential as an approach to their major problems. Since September 1939 practicing physicians, both military and civilian, have been turning more and more to the contributions of such research for help with the major illnesses which challenges medicine in this crisis. It has been found that about eighty per cent of the illness syndromes which cause disability in the armed forces, as well as in the industrial army, require a psychosomatic approach for adequate diagnosis and treatment.

According to the psychosomatic view, the criterion of health is maintenance by the organism of homeostatic equilibrium within itself and within its environmental field. Hence there is need for a new approach to classification of the subject matter of medicine, based on psychosomatic concepts. The major contributions to these concepts have come from physiologists on the one side and from medical psychologists on the other. But it has been difficult to establish common points of reference and common terms for these two disciplines. Traditional nosology is inadequate in both psychiatric and somatic phases, and there is little contact between their terminologies. The disease entities now recognized in each of these fields have little relevance either to the organism as a whole or to the *organism-environment continuum.*

What is needed is a system of classification which will aim, not at defining disease entities in the traditional sense, but rather at describing dynamic processes in ill persons. It should begin with the organism-environment continuum, and its material should relate to the flow of energy in a field of tension. It should lend itself to quantitative measurement, assuming that the appropriate techniques can be devised.

Thus, in the case of hypertension, the name should suggest the energy economy of the particular organism in its environmental situation, together with both behavioral and somatic symptoms. It should be capable of minor variation to parallel the minor variations of personality and symptom found within the general class. With such a nosology our thinking would be clarified and communication would be facilitated.

A well-adapted nomenclature is an aid to scientific progress. It is suggested that an adequate nosology can be best developed by the use of mathematical symbols such as are employed in the more mature sciences, like physics. This suggestion will be elaborated in another paper.

There is a habit of calling certain diseases psychosomatic in contradistinction to others. Some physicians think of psychosomatic medicine as a medical specialty parallel to internal medicine or psychiatry. But as a matter of fact, psychosomatic is merely an adjective which properly is applied to a method of approach useful in dealing with all types of human ailments, and essential to the diagnosis and treatment of some.

The dichotomy between psyche and soma which some feel is implied by the terms is the result of the way in which the scientific method in medicine has developed, and does not exist in the organism itself. The psychosomatic approach which represents a stereoscopic picture of the results of the two methods of observation should be valuable in dealing with all known diseases and even with some illness syndromes not yet recognized as disease entities.

There was a period in the history of civilization during which the major and often the only approach to the cure of disease was through the emotions. Methods of developing emotional attitudes in sick people were the most effective instruments in the therapeutic armamentarium of the medicine man and the witch doctor. With the progress of medical knowledge such techniques were called unscientific and were discouraged.

During the last four or five decades, a respectable body of scientific knowledge has been accumulated on which to base techniques for dealing with the psychic as well as with the somatic manifestations of dysfunction in the human personality.

Methods have been developed which will produce and cure neuroses in such animals as dogs, cats, sheep and rats, and it is known that disturbances in the energy economy of these animals may result in physiological as well as behavioral disorders, just as happens in human beings.

Any textbook incorporating the psychosomatic approach to medicine (three have been published within the last year; Weiss and English, 1943; Dunbar, 1943; and Hunt, 1944) includes an outline of the nature of dysfunction of the total personality and its manifestations in each organ system of the body, as well as a review of the personality types most susceptible to one or another of the well-known disease entities. It has become a platitude that "it is more important to know what kind of patient has the disease than what kind of disease the patient has."

As knowledge of physiological processes and sequences increases, more and more sequences are encountered which cannot be accurately observed or analyzed through the techniques of physiology alone. More complete understanding of them can be accomplished by a superposition of what can be observed by way of the techniques of physiology and by way of the techniques of psychology. Psychic and somatic phenomena take place in the same biological system and are probably two aspects of the same process.[1] All advances in medical knowledge probably should be reviewed in the light of recent developments in psychosomatic research.

Although infectious diseases are not generally reckoned in the eighty per cent of medical problems for which the psychosomatic approach is necessary, and although the application of bacteriological and physiological knowledge, with the aid of public health measures, has removed epidemiological diseases from among the first ten causes of mortality; colds and other infectious diseases are still responsible for a large percentage of labor wastage. Recent studies have shown that the psychosomatic approach is useful in dealing with these problems also. It is to be remembered that Osler said, "What happens to a patient with tuberculosis depends more on what he has in his head than on what he has in his chest." It is interesting also that the latest (14th) edition of Osler's *Principles and Practice of Medicine* (See Christian, 1942) has appeared with a first section devoted to psychosomatic medicine and functional diseases of the nervous system instead of the traditional chapter on infectious diseases. Earlier, in January 1939, occurred the initiation of the journal *Psychosomatic Medicine, Experimental and Clinical Studies*, was initiated.

[1] See Introductory Statement by the Editors, Psychosom. Med. **1**: 4, Jan. 1939.

The application of this point of view resulted in the inclusion of a discussion even of susceptibility to accidents in a recent colloquium on problems in psychosomatic medicine. It might be supposed that in infectious diseases, for instance, where the noxious agent is introduced from the environment, the personality has no rôle to play, and yet it is apparent even without careful study that this view ignores the factor of differential immunity. It might appear still more obvious that injuries resulting from accidents are caused solely by environmental impact, but psychosomatic study has revealed that this is far from the whole truth since it does not explain the well authenticated observation that some persons are far more prone to accidents than are others.

Maintenance of homeostatic equilibrium within the organism in its environmental field is essential for health and for efficiency. Sometimes the physiological aspect of a disturbance may be considered primary and physiological methods may be moderately effective, and the same is true of the psychological aspect and methods. But usually the best results are accomplished by a combination of the two.

II. *Psychosomatic approach to convalescence and rehabilitation.* Leading scientists and physicians are in general agreement as to psychosomatic concepts and the importance of their application to the problems confronting medicine today. Darwin wrote, "Without hypothesis there is no useful observation." Much needs to be worked out from the point of view of techniques, both medical and social, to make such application possible. More scientific studies correlating observations by way of physiological and psychological methods are needed, and physicians must be trained in the use of the stereoscopic picture thus obtained. Its place in diagnosis is described in Dunbar, 1943. Some suggestions as to its use in therapy are to be found in Weiss-English, 1943; Alexander, 1939; Saul, 1941; Dunbar-Arlow, 1944; and Hunt, 1944.

Although the psychosomatic approach has an application to all medical problems, it has a particular importance in relation to convalescence and rehabilitation. The chronic diseases which take their toll in the older age groups claim first place also as occasioning disability in the younger age groups, and their importance for both young and old increases in all times of crisis, economic and military. According to the statistics of the Metropolitan Life Insurance Company every other individual in the United States past the age of 50 years dies of cardiovascular-renal disease. From other sources we have evidence that probably half of these deaths are due to essential hypertension; that is, that almost one quarter of all people past the age of 50 years dies of the effects of hypertension on one or another of the vital

organs. Thus essential hypertension becomes the greatest problem of middle adult life, not even excepting cancer. (Weiss, 1939). And yet this important illness is one in which the causative agents are essentially unknown. But one thing we do know is that in this illness the emotional factors play an important and often a determining rôle.

Anyone inclined to give little heed to such statements as these because of a feeling that it is the young rather than the old who deserve medical protection, should consult the recent National Health Survey which has shown that nearly half of our sufferers from chronic disease are under 45 years of age, and 70 per cent of them are under 55. As a matter of fact only 15 per cent of all persons with chronic disease are over 65 years of age. Furthermore, other surveys have shown that the very illnesses which take their major toll in terms of death, disability, and invalidism in the older age groups are as prominent in proportion to total illness in younger age groups; for example, cardiovascular disease and accidents.

Already more than half of our patient-hospital days are devoted to the care of the chronically ill. Such patients require one half of the annual services of physicians and almost three fourths of the annual bedside nursing days. It is estimated that even now one out of five persons in the United States has some chronic disease, and that about two thirds of these are disabled for twelve months or more. It has been discovered that exacerbations of chronic illnesses are likely to occur in times of stress, and that they can be ameliorated or prevented by combined attention to psychic and somatic aspects of the illness. (See Dunbar, 1936–1938; Billings, 1937.) Rivers wrote, "Don't devote all your energy to the study of medicine; from time to time study a patient comprehensively and not merely according to existing medical curricula and horizons."

Aside from merely therapeutic considerations, the reduction of chronic disease and the shortening of convalescence on the part of sufferers from it, would eliminate a tremendous economic waste. Similar success in rehabilitation of returned service men suffering from disabilities would not only eliminate economic waste but would save the Federal budget many millions of dollars. (See, for example, reports on "The Hospital Survey for New York," 1937–1938.) Much the same principles are applicable to both types of cases. These principles involve understanding of the psychosomatic approach.

Fundamental to successful treatment is a will to get well on the part of the patient. Psychosomatic diagnosis has revealed that especially in chronic diseases, and even in fractures, there exists a will to be or to remain sick because the patient is using his illness as a means of escaping responsibility, unpleasant life situations, or internal conflict with which he does not know how to deal otherwise. This statement does not imply the existence of conscious malingering. To state what occurs, in more physiological terms, when the energy released in the patient by external stimulus or internal conflict is mobilized for action but no appropriate action is taken, it is likely to become bound in somatic symptoms, and the tension, instead of being dissipated in appropriate behavior, continues to disturb internal homeostasis.

Returned soldiers are influenced not only by the ordinary motives to find their release in pathological symptoms, but they are also driven in this direction by special difficulties of their own. While enduring the abnormal traumata and pressures of war, they have idealized their lives at home and have also developed an expectation that they deserve extraordinary rewards on returning to civilian life (Kubie, 1944).

When they discover that home is not all they imagined it to be and that they must resume the dull civilian routine without special consideration, they frequently regress to the attitude of the infant who insists on being cared for, and of course being sick renders this care necessary. In addition, governmental support or compensation during illness may remove much of the incentive for recovery if this attitude is uncorrected.

In dealing with the emotional origin of symptoms the most important goal for the physician is the development of insight in the patient concerning the way in which he deals with his unsolved conflicts, or his unacknowledged reasons for being sick. In this endeavor, it is exceedingly important to avoid any encouragement of the guilt and anxiety which are usually already present. Often spontaneous statements on the part of the patient will reveal to him the real meaning of his symptoms. When insight is once achieved, the patient, with the doctor's assistance, may be able to learn a better method of dealing with what has disturbed him and so cease to need the symptom. This, combined with whatever ordinary medical routine is required, often will go far toward shortening convalescence.

A case which illustrates these points was that of a patient who was suffering from an obscure heart ailment and on three different occasions was hospitalized with such severe attacks that she had to be kept in an oxygen tent. After insight was developed she completely recovered, and has had no recurrence over a period of six years. Concerning her illness, this patient said: "Until you made me face what was really bothering me, and showed me I could do something about it, life was impossible except when I was sick. It may sound funny to you, but it used to be a relief to have a real pain to fight, instead of my husband, and all the people I hated

and felt despised me. What I used to call the knife in my heart hurt so much that it blotted out everything else, everything that bothered me. It was like being drunk but even more potent."

III. *Conclusion.* The great physiological advances of recent years have made possible the development of psychosomatic medicine by showing the association between emotions and bodily processes. Without simultaneous consideration of both it is impossible to make much headway with convalescence in that group of diseases which now accounts for by far the heaviest burden of mortality and morbidity. The same techniques are applicable to the rehabilitation of service men and women. Medical psychology has developed the techniques for doing so. They involve development in the patient of insight regarding the relationship between his emotional conflicts and his symptoms, an insight which makes possible the will to get well. If this goal is achieved, the patient's anxiety is relieved and he is able to assist the physician in shortening the period of convalescence. Without this cooperation, recovery is always retarded and it is sometimes impossible.

As Gatti wrote, "Quand on est malade, c'est une dispute entre le malade et la maladie" (*Histoires Médicales*). When both the patient and the physician realize this, their co-operative achievement as a team in conquering disease is enormously increased.

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ANNUAL MEETING
CLEVELAND, MAY 8, 9, 10, 1945

The last Annual Meeting was held in Boston in 1942. At the request of the Office of Defense Transportation the Executive Committee voted to dispense with the Annual Meetings scheduled for 1943 and 1944. The Executive Committee now feels, and has so voted, that the best interests of the Federation will be jeopardized should a third consecutive Annual Meeting be cancelled.

Nevertheless, transportation and hotel facilities are still heavily burdened. To meet this situation as far as may be at the present time, the Executive Committee, in collaboration with the Cleveland Local Committee, has planned the meeting for the mid-week, Tuesday, Wednesday and Thursday, with provision for scientific sessions and business meetings in the evening.

Provisional arrangements for the meeting by the Local Committee are given below. Final arrangements will be published in the program section of the next issue.

CLEVELAND MEETING

The Federation will meet in Cleveland May 8, 9, 10, 1945. At present the Executive Committee of the Federation and the Local Committee are planning to streamline this meeting in conformity with wartime conditions. Scientific and business meetings will be held Tuesday and Wednesday mornings, afternoons and evenings and Thursday morning and afternoon. Monday will be devoted to Council and Executive Committee meetings and to registration.

HEADQUARTERS AND MEETING PLACES. The headquarters of the constituent societies will be grouped in two hotels as follows:

Hotel Cleveland

American Physiological Society
American Society for Experimental Pathology
American Association of Immunologists

Hotel Statler

American Society of Biological Chemists
American Society for Pharmacology and Experimental Therapeutics
American Institute of Nutrition

As far as possible, all scientific sessions of each society will be held in the headquarters hotel designated. The Federation Joint Session and the motion picture demonstrations will be held at the Hotel Statler. Programs and additional announcements will be published in the March issue of the Federation Proceedings.

The Local Committee wishes to express an earnest desire to assist in the arrangement of group dinners or group gatherings during the period of the meetings. The Local Committee will gladly make all preliminary arrangements and sell tickets, if desired, but all guarantees and other obligations must be assumed by the society or group involved. Such arrangements should be made in advance of the meetings. Information regarding suitable location, probable menus and prices for group luncheons and dinners may be obtained by writing to the Secretary of the Local Committee.

The Annual Dinner of the Society for Pharmacology and Experimental Therapeutics will be held on Thursday evening. The Circulation Group will also arrange a program-dinner on Thursday evening

It is planned to have an informal smoker Tuesday evening following the business meetings.

REGISTRATION. Registration will start Monday, 12 noon, May 7th, at both of the headquarters hotels. A person who is a member of any of the constituent societies of the Federation registers as a Member. Individuals from any recognized biological laboratory may enroll as Associate Members of the Federation for the meeting. A registration fee of one dollar will be required from each Member and Associate Member. *Admittance to the scientific sessions is restricted to persons so registered.* Registrants accompanied by members of their immediate family who are not eligible for registration may obtain guest privileges for them at the time of registration. Programs and abstracts will be on sale at the registration desks.

HOTEL RESERVATIONS. Each person should make his or her own hotel reservation, indicating the time of arrival and departure. *It is important to state that the room is desired for the Federation Meetings and it is essential that hotel reservations be made before April 15, 1945.* The Local Committee has fairly adequate room guarantees for persons attending the Federation Meetings. However, because of the heavy strain placed upon hotels at this time they cannot promise reservations for the Federation Meetings after April 15, 1945.

The following prices per room have been quoted for the meetings:

R & Z Library

DOWNTOWN

Hotel Cleveland, Public Square—Single, $3.00–5.00, Double, $4.50–7.00. Twin Bed, $6.00–10.00, Suites, 4 persons, $20.00.

Hotel Statler, Euclid, E. 12th—Single, $3.00–4.50, Double, $5.00–6.50, Twin Bed, $5.00–8.00, Suites (4 persons), $10.00–15.00.

Hotel Carter, Prospect near E. 9th—Single, $3.50–4.50, Double, $5.50–6.50, Twin Bed, $6.00–7.00.

Hotel Hollenden, Superior, E. 6th—Single, $3.50–5.50, Double, $5.00–8.00; Twin Bed, $6.00–8.00.

New Amsterdam, Euclid, E. 22nd—Single, $1.50–2.50, Double, $2.00–4.50.

Hotel Auditorium, Opposite Public Auditorium—Single, $2.75–3.00; double, $4.50–5.00.

Hotel Olmsted, Superior, E. 9th—Single, $3.00, Double, $6.00.

EAST SIDE

Tudor Arms Hotel, Carnegie, E. 107th—Single, $3.50–7.50; Double, $6.00–11.00.

Fenway Hall, Euclid, E. 107th—Single, $3.50; Double, $6.00.

Wade Park Manor, Park Lane, E. 107th—Single, $3.00–4.50; Double, $5.00–6.50.

All of the downtown hotels are within easy walking distance of each other. The walk between the two headquarters hotels can be made easily in ten minutes; however, there are convenient, frequent and cheap street car and taxi services between the hotels. It will facilitate accommodation of the maximum number of registrants if as many persons as possible will double up in making room reservations.

DEMONSTRATIONS AND MOTION PICTURES. (a) *Static Demonstrations*. Due to difficulties of transportation and of making suitable arrangements during wartime, the static demonstrations will be omitted this year.

(b) *Motion Picture Demonstrations* will be shown at the Hotel Statler. Each motion picture will be shown several times during the sessions by an operator provided by the Local Committee, according to the schedule to be announced by the Local Committee. Demonstrators may explain their motion pictures or provide mimeographed sheets in explanation, if needed.

Only 16 mm. film can be shown; films that do not conform to the usual underwriter's conditions for home exhibition cannot be shown. *Motion pictures cannot be shown at scientific sessions and only those officially announced in the program will be run.*

The Secretary of the Local Committee must be notified as to the title, authorship, *time of run*, and *size of reel*, before March 15, 1945.

CLEVELAND LOCAL COMMITTEE

General Chairman: C. J. Wiggers.

Sub-committee Chairmen: H. Goldblatt (Reception, Registration, Information, Hotels); J. P. Quigley (Meeting Places); A. D. Welch (Public Information).

Secretary: H. D. Green.

Treasurer: A. Sidney Harris.

General Committee: Torald Sollmann, H. T. Karsner, V. C. Myers, C. J. Wiggers.

Sub-committees: Reception, Registration, etc.: H. Goldblatt, A. H. Free, E. E. Ecker, H. Chase, J. W. Price, J. R. Leonards, D. F. Opdyke, L. Peters, I. H. Page. *Meeting Places, etc.:* J. P. Quigley, A. S. Harris, R. I. Dorfman, J. W. Mull, R. Dominguez, R. L. Thompson, E. E. Selkurt, E. B. Bueding, C. A. Kuether, A. C. Corcoran.

To avoid confusion, address all inquiries to the Secretary of the Local Committee, Dr. Harold D. Green, Dept. of Physiology, School of Medicine, Western Reserve University, Cleveland 6, Ohio.

THE HARVARD APPARATUS COMPANY, THE AMERICAN JOURNAL OF PHYSIOLOGY, AND DR. W. T. PORTER

The undersigned, having on the request of W. T. Porter assumed the guidance of the Harvard Apparatus Company, wish to place on record Dr. Porter's unique services to Science. Some forty-five years ago, when there was scant if any laboratory teaching of physiology in our colleges and universities outside the medical schools, and laboratory teaching of physiology in medical schools was just emerging, Dr. Porter saw the probable importance of rendering available to our colleges, universities and medical schools good standard apparatus at the lowest possible cost for the laboratory teaching of physiology. Dr. Porter started the Harvard Apparatus Company as a private corporation, partly on borrowed funds. This business has been conducted by Dr. Porter in the public interest, and without commercial profit. When there was a modest annual surplus, this was used: (a) to improve production equipment, (b) to provide a pension fund for the Company's employees, and (c) to finance the W. T. Porter Research Fellowship in Physiology, administered by the Council of the American Physiological Society. We intend to continue these

policies. The research fellowship was started by Dr. Porter in 1920, and to date the Harvard Apparatus Company has paid to the American Physiological Society approximately $28,000 for this Fellowship Fund. So far this annual fellowship has been awarded to qualified young investigators working in well equipped laboratories in the United States and in Canada. We feel sure that the Council of the American Physiological Society will give due consideration to applications from qualified young investigators working in well equipped laboratories in other countries.

In 1929 Dr. Porter offered the Harvard Apparatus Company as a free gift to the American Physiological Society. The Society did not consider it feasible to undertake the management of the Company. But the Council of the Society at that time said: "There is no one agency, during recent years, which has contributed more to the sound teaching in experimental physiology in this country than has the Harvard Apparatus Company."

In 1934 the Harvard Apparatus Company was reorganized as a non-profit corporation under the laws of the State of Massachusetts "for the promotion of teaching and research in physiology and its allied sciences." Dr. Porter gave to this corporation all property owned by the private Harvard Apparatus Company corporation. Dr. Porter has received no salary for his services to the corporation. We intend to follow Dr. Porter's example, with (we hope) some of Dr. Porter's efficiency and vision. In recent years the services to the sciences of functional biology rendered by Dr. Porter within our own borders have been extended to many other countries. The services of the Company can be further extended to the liberal arts colleges, junior colleges, and high schools where experimental physiology has not yet been introduced as an element of a liberal education, a foward step in the education of tomorrow, probably in the cards.

Forty-six years ago Dr. W. T. Porter founded The American Journal of Physiology (for the publication of research), and for 16 years he carried the entire financial responsibility and editorial burden for the first 33 volumes, that is, until 1914, when Dr. Porter presented this Journal (including back volumes in stock) as a gift to the American Physiological Society.

These are significant services to science and to our fellow men. They call for more than a passing note, as they echo and amplify the voice of the English chemist, James Smithson of a hundred years ago, whose vision of science, whose faith in man, and whose material wealth established the Smithsonian Institution of Washington, *"for the increase and diffusion of knowledge among men."*

A. J. Carlson, *Chairman*
University of Chicago
Philip Bard
Johns Hopkins University
Walter E. Garrey
Vanderbilt University
F. W. Weymouth
Stanford University
Maurice B. Visscher
University of Minnesota

RENEWED ANTIVIVISECTION THREAT

A Report by the Committee on Defense of Biological Research

G. H. Whipple, *Acting Chairman*, A. B. Luckhardt and C. I. Reed, *Secretary*

For many years it has been the policy of the experimental biologists to give cognizance to the existence of the antivivisectionists' activities only when they have constituted overt legislative threats to the freedom of scientific research.

The relative ease and speed with which these attacks have been disposed of in most instances has tended to minimize the potentially serious nature of the antivivisection movement.

When one considers the cost in energy and money involved in defeating the proposed Humane Pound Law in California in 1937, and in the almost continuous legislative battles in Chicago extending over a period of nearly twenty years, one becomes impressed with the possibility that what has happened in England and in some sections of this country may be extended to the country as a whole.

The Committee on Defense of Biological Research was appointed by the Executive Committee of the Federation. This Committee has been given no mandatory powers, nor any specific instructions. At first, there were no funds available for its use, but later the Physiological Society agreed that the Committee could draw on its Treasury to the extent of $250.00 annually. Actually, the draft has never exceeded $50.00 in any one year, and has usually been much less.

The first Chairman of the Committee, Dr. Elliott C. Cutler, now on leave with the overseas forces, has served also as Chairman of a similar but somewhat larger committee of the American Medical

Association. No distinction can be made in the work of these two groups as the Chairman has called upon the membership and the available facilities of both, as circumstances have indicated. The personnel of both groups has functioned in close co-operation with the Bureau of Health Education and the Bureau of Legal Medicine of the American Medical Association, which has rendered indispensable service as a legal adviser.

During the period of existence of the Committee on Defense of Biological Research, the combined group has participated in some manner in the defeat or neutralization of proposed restrictive legislation in 33 instances, either in Congress, in state legislatures or in various cities. The extent of participation has varied in character and importance. In most instances, its functions have been limited to advice on legislative procedure, information on sources of campaign literature, supplying such literature from existing files of reprints and pamphlets and writing special material more suitable for particular occasions. In other instances, members of the group, or others whose services were especially requested, have participated directly as speakers or consultants in local activities. In a few cases assistance has been rendered in securing funds to be used by our colleagues in local campaigns. In two instances restrictive bills were introduced somewhat surreptitiously into state legislatures without having been discovered by the experimentalists residing in those states. In one of these cases the bill was never called for a hearing. In the other it was withdrawn by the proponent. In both instances Committee activity was a decisive factor.

Sometimes, local groups have desired to work independently. And it is impossible for the Committee to function importantly where strong local organizations exist, such as the Illinois Society for the Protection of Medical Research or the corresponding organization in California. On the other hand, local groups never previously involved in such a fight, and therefore not organized in advance or prepared by experience, have profited greatly from the assistance the Committee was able to render. Full credit is extended to each person, whether a member of either Committee, or a local resident who has co-operated by supplying information about influential factors which might be utilized, or in some other decisive manner. It is impossible to give a comparative evaluation of the work of individuals. It can only be stated that they have co-operated in the total efforts and that the results of those efforts have been, in general, favorable to the continued pursuit of research.

But all of this activity has been of a purely defensive nature. Furthermore, there does not exist anywhere in the world any provision actually legalizing experimental investigations on living subjects, except the state law in Nebraska which legalizes work on animals but does not provide any authorization for securing them. While there are ordinances in many cities *permitting* the use of impounded dogs for experimental purposes, even these do not legalize the experimental procedures.

When the situation in California became so acute in 1937, Dr. Cutler took the stand that the traditional defensive attitude should be abandoned in favor of aggressive positive action. Accordingly, he directed that a model law should be drafted which would, after the manner of the Anatomical Materials Acts in force in all states where medical schools exist, remove this problem from local control, and make mandatory the surrender of unclaimed material available in any city in the state. Such a model law was prepared and has been examined and revised by several groups of legal advisers until it appears to be adaptable to any situation, national, state or urban. Plans were well under way to introduce it into Congress in 1941, but the war intervened. Previously, efforts had been made to have the bill put through in California and Wisconsin, but local groups felt it inadvisable to undertake the project because of the probable magnitude of the cost. However, the model is still available to anyone desiring to use it.

The use of impounded dogs is legalized by ordinance in Chicago, St. Louis, Louisville, Detroit, Dallas, Houston, Galveston and possibly a few other places. But even this does not insure that the animals will be available, nor does it insure that a researcher will not be prosecuted under other existing legislation.

This total situation renders the position of the experimental biologists especially vulnerable. In a recent hearing before the Chicago City Council the above cities were referred to in such highly uncomplimentary terms that it was necessary to refute the argument by pointing out that in other cities where legal provisions have not been made for the use of locally impounded dogs, it has been necessary to secure dogs at greater cost from other sources of supply. Where dogs have been secured from contract dealers, there can be no assurance that the latter are legally entitled to sell them.

Numerous attempts have been made to have legislation adopted in Congress which would not only prevent the use of dogs in the medical schools in the District of Columbia and in all federal institutions wherever located, but some of the measures would have prohibited all experimental work on all sub-human forms of life. The latter objective we know to be the avowed ultimate goal of all antivivisectionist activity. After the disastrous attempt on the part of the National Antivivisection Society in 1929 to have adopted by the legislature of Illinois a bill of such extreme

nature, the Courtney bill, the strategy of all organizations furthering antivivisection measures has been to confine all immediate efforts to restricting or abolishing the use of dogs. However, a perusal of bulletins of the various antivivisectionist groups reveals that the original purpose, first announced nearly a century ago, has never been abandoned. Once they have accomplished the prohibition of the use of dogs, they will, by a process of attrition, secure prohibition of the use of other species, one by one.

The antivivisectionists have the advantage that they can and do operate on a national scale, with the support of huge endowments and with full time executives. We experimental biologists have no agency through which we can carry on a sustained educational program on a national scale. Only when extreme emergencies arise do we devote time and energy to our own group interests, and then only at the expense of our official duties and often with only casual support and little encouragement from administrative officers of the educational institutions supporting scientific research and profiting by the results thereof.

Furthermore, the national antivivisectionists' organizations participate actively in all local legislative efforts, whereas the experimental biologists have no national agency representing all branches of their efforts and are not equipped to participate in local activities to any greater extent than has already been indicated. Some local groups have even resented and resisted any effort on our part to assist them. Unfortunately, many local groups seem to be indifferent to restrictions and misfortunes befalling other local groups.

It is true that some well organized local groups, such as the Chicago Scientific Association, are better able to cope with a purely local situation than any existing national agency. It is equally true, however, that any such group can profit greatly by being able to cite active support from any such national agency or from other isolated groups. This fact, therefore, does not argue against a national educational program designed to acquaint an enlightened citizenry with accomplishments in health conservation through animal experimentation and to emphasize the importance of freedom of scientific research. It is being suggested to writers of scientific articles for lay publications that in all releases of scientific information some emphasis should be given to the place of animal experiments in the development of new information.

Neither the lay voters nor the legislators are *yet* fully aware of the indispensability of animals for the advances which have been made or are to be made. The latter group are particularly naive in failing to comprehend the seriousness of their casual support of measures ingeniously disguised as humane legislation.

On January 6, 1943, Representative Burdick introduced into the lower House of Congress a frank antivivisection bill which provides absurdly drastic penalties for trivial violation. A companion bill was introduced by Senator Langer into the Senate on January 18th. Immediately, through the agency of our Committee, the North Dakota Medical Association was activated to take cognizance. As a result, the measure has remained immobilized. Several agencies are carefully examining any activity presaging revival of interest in this measure by its proponents.

It is certain that any type of proposed antivivisection legislation can be defeated in Congress or in local communities where medical schools and research institutes exist, provided the local biologists and physicians present a strong opposition. However, in certain states where such opposition is difficult to marshal the Antivivisectionists *could* be successful. Their success in a number of such states would obviously help their cause considerably. Their cause is now abetted by the fact that in many cities they are able to obtain and to destroy all unclaimed stray animals.

The fact that thousands of cats and dogs are destroyed by antivivisectionists, when they could be used for research and teaching and when they have to be secured by other means in most cities, should constitute a moral challenge to experimental biologists. If our work is important for public welfare, why should we and an informed public permit the animals to be wantonly destroyed, and why should we be hampered in our work by lack of research material? Are the Antivivisectionists, S.P.C.A. and similar organizations so well entrenched in some of our cities that unclaimed animals cannot be secured for teaching and research?

These questions have been asked to provoke thought and to indicate the problems involved if animal experimentation is to be elevated to the point where it is legalized or regarded by communities as sufficiently important to warrant the utilization of unclaimed impounded animals.

Your Committee feels that to some extent it has been able to assist in antivivisection campaigns. However, it feels that it has not contributed and is not in a position to contribute as much as the issue requires.

In conclusion, the Committee believes it is appropriate to inquire whether its existence is justified by those activities which it is able to conduct, namely, to use the name of the Federation in support of animal experimentation in local antivivisection campaigns and to supply literature and advice when it is requested by local groups of biologists. It is hoped that concrete suggestions

as to other methods of procedure may be presented at the next meeting of the Federation. Meantime, attention is called to the plan now under consideration by the Association of American Medical Colleges for the establishment of a full time bureau to take over the functions of the Committee of the Federation and of the American Medical Association, and to enlarge support by bringing in other agencies and mechanisms not now integrated.

No organization can accomplish much aggressive action or even hold off encroachments without the enthusiastic support, not only of the constituent societies in the Federation, but of all of the medical organizations, the dental and pharmaceutical groups, nutritionists, the American Association for the Advancement of Science and the food industries. With such support, a central agency such as has been proposed, *could* be much more effective and *could* do much to safe-guard biological research.

EXECUTIVE COMMITTEE, 1944

PHILIP BARD, WALLACE O. FENN, The Physiological Society

E. A. DOISY, ARNOLD K. BALLS, The Biochemical Society

ERWIN E. NELSON, RAYMOND N. BIETER, The Pharmacological Society

BALDUIN LUCKÉ, H. P. SMITH, The Pathological Society

ICIE MACY-HOOBLER, ARTHUR H. SMITH, The Institute of Nutrition

JACQUES J. BRONFENBRENNER, ARTHUR F. COCA, The Association of Immunologists

PHILIP BARD, *Chairman*, Johns Hopkins Medical School, Baltimore 5, Md.

ALBERT G. HOGAN, *Ex-Chairman*

D. R. HOOKER, *Secretary*, 19 W. Chase St., Baltimore 1, Md.

STANDING COMMITTEES

Defence of Biological Research: ELLIOTT C. CUTLER, *Chairman;* GEORGE H. WHIPPLE, *Acting Chairman;* A. B. LUCKHARDT, C. I. REED.

International Congresses: H. S. GASSER, Physiology, *Chairman;* A. J. CARLSON, Physiology; D. D. VAN SLYKE, Biochemistry; E. K. MARSHALL, JR., Pharmacology; PEYTON ROUS, Pathology; L. A. MAYNARD, Nutrition; J. J. BRONFENBRENNER, Immunology.

Public Information: HARRY GOLDBLATT, *Chairman;* R. G. HOSKINS, R. W. GERARD.

Placement Service: H. B. LEWIS, *Director.*

Representatives, Council A.A.A.S.: G. PHILIP GRABFIELD, CHARLES G. KING.

Federation Proceedings, Control Committee: PHILIP BARD, *Chairman;* C. G. KING, ARTHUR P. LOCKE, MORTON MCCUTCHEON, C. F. SCHMIDT, A. H. SMITH.

FORMER EXECUTIVE COMMITTEES

Philadelphia, Dec. 28–31, 1913

S. J. MELTZER, *Chairman*, and A. J. CARLSON, *Secretary*, The Physiological Society. A. B. MACALLUM and P. A. SHAFFER, The Biochemical Society. T. SOLLMANN and J. AUER, The Pharmacological Society.

St. Louis, Dec. 27–30, 1914

G. LUSK, *Chairman*, and P. A. SHAFFER, *Secretary*, The Biochemical Society. T. SOLLMAN and J. AUER, The Pharmacological Society. R. M. PEARCE and G. H. WHIPPLE, Thh Pathological Society. W. B. CANNON and A. J. CARLSON, The Physiological Society.

Boston, Dec. 26–29, 1915

TORALD SOLLMANN, *Chairman*, and JOHN AUER, *Secretary*, The Pharmacological Society. THEOBALD SMITH and PEYTON ROUS, The Pathological Society. W. B. CANNON and C. W. GREENE, The Physiological Society. WALTER JONES and P. A. SHAFFER, The Biochemical Society.

New York, Dec. 27–30, 1916

SIMON FLEXNER, *Chairman*, and PEYTON ROUS, *Secretary*, The Pathological Society. W. B. CANNON and C. W. GREENE, The Physiological Society. WALTER JONES and STANLEY R. BENEDICT, The Biochemical Society. REID HUNT and J. AUER, The Pharmacological Society.

Minneapolis-Rochester, Dec. 27–29, 1917

FREDERIC S. LEE, *Chairman*, and CHARLES W. GREENE, *Secretary*, The Physiological Society. CARL L. ALSBERG and STANLEY R. BENEDICT, The Biochemical Society. REID HUNT amd L. G. ROWNTREE, The Pharmacological Society. LUDVIG HEKTOEN and HOWARD T. KARSNER, The Pathological Society.

Baltimore, April 24–26, 1918

CARL L. ALSBERG, *Chairman*, and STANLEY R. BENEDICT, *Secretary*, The Biochemical Society. REID HUNT and E. D. BROWN, The Pharmacological Society. H. GIDEON WELLS and HOWARD T. KARSNER, The Pathological Society. FREDERIC S. LEE and CHARLES W. GREENE, The Physiological Society.

Cincinnati, Dec. 29–31, 1919

A. S. LOEVENHART, *Chairman*, and E. D. BROWN, *Secretary*, The Pharmacological Society. W. G. MACCALLUM and HOWARD T. KARSNER, The Pathological Society. WARREN P. LOMBARD and CHARLES W. GREENE, The Physiological Society. STANLEY R. BENEDICT and VICTOR C. MYERS, The Biochemical Society.

Chicago, Dec. 28–30, 1920

WILLIAM H. PARK, *Chairman*, and HOWARD T. KARSNER, *Secretary*, The Pathological Society. WARREN P. LOMBARD and CHARLES W. GREENE, The Physiological Society. STANLEY R. BENEDICT and VICTOR C. MYERS, The Biochemical Society. A. S. LOEVENHART and EDGAR D. BROWN, The Pharmacological Society.

New Haven, Dec. 28–30, 1921

J. J. R. MACLEOD, *Chairman*, and CHARLES W. GREENE, *Secretary*, The Physiological Society. D. D. VAN SLYKE and VICTOR C. MYERS, The Biochemical Society. C. W. EDMUNDS and EDGAR D. BROWN, The Pharmacological Society. F. G. NOVY and WADE H. BROWN, The Pathological Society.

Toronto, Dec. 27–29, 1922

D. D. VAN SLYKE, *Chairman*, and VICTOR C. MYERS, *Secretary*, The Biochemical Society. C. W. EDMUNDS and EDGAR D. BROWN, The Pharmacological Society. HOWARD T. KARSNER and WADE H. BROWN, The Pathological Society. J. J. R. MACLEOD and CHARLES W. GREENE, The Physiological Society.

St. Louis, Dec. 27–29, 1923

C. W. EDMUNDS, *Chairman*, and EDGAR D. BROWN, *Secretary*, The Pharmacological Society. E. L. OPIE and WADE H. BROWN, The Pathological Society. A. J. CARLSON and CHARLES W. GREENE, The Physiological Society. PHILIP A. SHAFFER and VICTOR C. MYERS, The Biochemical Society.

Washington, Dec. 29–31, 1924

ALDRED S. WARTHIN, *Chairman*, and E. B. KRUMBHAAR, *Secretary*, The Pathological Society. A. J. CARLSON and WALTER J. MEEK, The Physiological Society. P. A. SHAFFER and D. WRIGHT WILSON, The Biochemical Society. JOHN AUER and E. D. BROWN, The Pharmacological Society.

Cleveland, Dec. 28–30, 1925

A. J. CARLSON, *Chairman*, and WALTER J. MEEK, *Secretary*, The Physiological Society. H. C. SHERMAN and D. WRIGHT WILSON, The Biochemical Society. JOHN AUER and E. D. BROWN, The Pharmacological Society. GEORGE H. WHIPPLE and E. B. KRUMBHAAR, The Pathological Society.

Rochester, N. Y., April 14–16, 1927

E. C. KENDALL, *Chairman*, and F. C. KOCH, *Secretary*, The Biochemical Society. JOHN AUER and E. D. BROWN, The Pharmacological Society. W. H. BROWN and E. B. KRUMBHAAR, The Pathological Society. J. ERLANGER and W. J. MEEK, The Physiological Society.

Ann Arbor, April 12–14, 1928

CARL VOEGTLIN, *Chairman*, and E. D. BROWN, *Secretary*, The Pharmacological Society. DAVID MARINE and CARL V. WELLER, The Pathological Society. JOSEPH ERLANGER and WALTER J. MEEK, The Physiological Society. E. V. MCCOLLUM and D. WRIGHT WILSON, The Biochemical Society.

Boston, Aug. 19–24, 1929

(The XIIIth International Physiological Congress)

EDWARD B. KRUMBHAAR, *Chairman*, and CARL V. WELLER, *Secretary*, The Pathological Society. JOSEPH ERLANGER and WALTER J. MEEK, The Physiological Society. E. V. MCCOLLUM and D. WRIGHT WILSON, The Biochemical Society. CARL VOEGTLIN and E. D. BROWN, The Pharmacological Society.

Chicago, March 26–29, 1930

WALTER J. MEEK, *Chairman*, and ALFRED C. REDFIELD, *Secretary*, The Physiological Society. W. R. BLOOR, and HOWARD B. LEWIS, The Biochemical Society. CARL VOEGTLIN and E. D. BROWN, The Pharmacological Society. WILLIAM F. PETERSEN and CARL V. WELLER, The Pathological Society.

Montreal, April 8–11, 1931

W. R. BLOOR, *Chairman*, and H. B. LEWIS, *Secretary*, The Biochemical Society. GEORGE B. WALLACE and E. D. BROWN, The Pharmacological Society. FREDERICK L. GATES and C. PHILLIP MILLER, The Pathological Society. WALTER J. MEEK and ARNO B. LUCKHARDT, The Physiological Society.

Philadelphia, April 27–30, 1932

GEORGE B. WALLACE, *Chairman*, and V. E. HENDERSON, *Secretary*, The Pharmacological Society. SAMUEL R. HAYTHORN and C. PHILLIP MILLER, The Pathological Society. WALTER J. MEEK and ARNO B. LUCKHARDT, The Physiological Society. H. C. BRADLEY and HOWARD B. LEWIS, The Biochemical Society.

Cincinnati, April 10–12, 1933

PEYTON ROUS, *Chairman*, and C. PHILLIP MILLER, *Secretary*, The Pathological Society. ARNO B. LUCKHARDT and FRANK C. MANN, The Physiological Society. H. C. BRADLEY and HOWARD B. LEWIS, The Biochemical Society. WM. DEB. MACNIDER and V. E. HENDERSON, The Pharmacological Society.

New York, March 28–31, 1934

ARNO B. LUCKHARDT, *Chairman*, FRANK C. MANN, *Secretary*, and ALEXANDER FORBES, *Treasurer*, The Physiological Society. W. M. CLARK and H. A. MATTILL, The Biochemical Society. W. DEB. MACNIDER and V. E. HENDERSON, The Pharmacological Society. CARL V. WELLER and C. PHILLIP MILLER, The Pathological Society.

Detroit, April 10–13, 1935

W. M. CLARK, *Chairman*, H. A. MATTILL, *Secretary*, and C. H. FISKE, *Treasurer*, the Biochemical Society. CHARLES W. GREENE and FRANK C. MANN, The Physiological Society. R. A. HATCHER and E. M. K. GEILING, The Pharmacological Society. S. BURT WOLBACH and SHIELDS WARREN, The Pathological Society.

Washington, March 25–28, 1936

V. E. HENDERSON, *Chairman*, E. M. K. GEILING, *Secretary*, and C. M. GRUBER, *Treasurer*, The Pharmacological Society. FRANK C. MANN and ANDREW C. IVY, The Physiological Society. H. B. LEWIS and H. A. MATTILL, The Biochemical Society. OSKAR KLOTZ and SHIELDS WARREN, The Pathological Society.

Memphis, April 21–24, 1937

ALPHONSE R. DOCHEZ, *Chairman*, and SHIELDS WARREN, The Pathological Society. FRANK C. MANN and ANDREW C. IVY, The Physiological Society. HOWARD B. LEWIS and H. A. MATTILL, The Biochemical Society. V. E. HENDERSON and E. M. K. GEILING, The Pharmacological Society. D. R. HOOKER, *Secretary*.

Baltimore, March 30–April 2, 1938

WILLIAM T. PORTER, *Honorary President;* WALTER E. GARREY, *Chairman*, and ANDREW C. IVY, The Physiological Society. GLENN E. CULLEN and H. A. MATTILL, The Biochemical Society. ARTHUR L. TATUM and G. PHILIP GRABFIELD, The Pharmacological Society. C. PHILLIP MILLER and PAUL R. CANNON, The Pathological Society. D. R. HOOKER, *Secretary*.

Toronto, April 26–29, 1939

GLENN E. CULLEN, *Chairman*, and CHARLES G[.] KING, The Biochemical Society. ARTHUR [L.] TATUM and G. PHILIP GRABFIELD, The Pharmac[o]logical Society. C. PHILLIP MILLER and PAUL [R.] CANNON, The Pathological Society. WALTER [R.] GARREY and ANDREW C. IVY, The Physiologic[al] Society. D. R. HOOKER, *Secretary*.

New Orleans, March 13–16, 1940

E. M. K. GEILING, *Chairman*, and G. PHILI[P] GRABFIELD, The Pharmacological Society. ERNES[T] W. GOODPASTURE and PAUL R. CANNON, Th[e] Pathological Society. ANDREW C. IVY and PHILI[P] BARD, The Physiological Society. WILLIAM C[.] ROSE and CHARLES G. KING, The Biochemic[al] Society. D. R. HOOKER, *Secretary*.

Chicago, April 15–19, 1941

SHIELDS WARREN, *Chairman*, and H. P. SMITH, The Pathological Society. THORNE M. CARPENTER and L. A. MAYNARD, The Institute of Nutrition. ANDREW C. IVY and PHILIP BARD, The Physiological Society. WILLIAM C. ROSE and CHARLES G. KING, The Biochemical Society. E. M. K. GEILING and G. PHILIP GRABFIELD, The Pharmacological Society. D. R. HOOKER, *Secretary*.

Boston, March 31, April 1, 2, 3, 4, 1942

ALBERT G. HOGAN, *Chairman*, and ARTHUR H. SMITH, The Institute of Nutrition. PHILIP BARD and CARL J. WIGGERS, The Physiological Society. RUDOLPH J. ANDERSON and ARNOLD K. BALLS, The Biochemical Society. E. M. K. GEILING and R. N. BIETER, The Pharmacological Society. JESSE L. BOLLMAN and H. P. SMITH, The Pathological Society. SHIELDS WARREN, *Ex-Chairman*. D. R. HOOKER, *Secretary*.

1943, 1944: The meetings scheduled for Cleveland were cancelled because of war conditions

PHILIP BARD, *Chairman*, and WALLACE O. FENN, The Physiological Society. E. A. DOISY and ARNOLD K. BALLS, The Biochemical Society. E. K. MARSHALL, JR. and RAYMOND N. BIETER, The Pharmacological Society. BALDUIN LUCKÉ and H. P. SMITH, The Pathological Society. LEONARD A. MAYNARD and ARTHUR H. SMITH, The Institute of Nutrition. JACQUES J. BRONFENBRENNER and ARTHUR F. COCA, The Association of Immunologists.

FEDERATION BY-LAWS

BY-LAWS

Adopted at the Washington Meeting, 1936 and amended at the Boston Meeting, 1942

1. The Presidents and Secretaries of the Constituent Societies, the Chairman of the Executive Committee of the preceding year and the Federation Secretary shall form the Executive Committee of the Federation.

2. The Chairmanship of the Executive Committee shall be held in turn by the Presidents of the Constituent Societies, who shall succeed one another annually in the order of seniority of the Societies.

3. The Executive Committee shall appoint annually from the membership of the Federation a secretary-treasurer, to be known as the Federation Secretary.

4. The Federation Secretary shall: (a) Keep the minutes of the Executive Committee and distribute copies to the Secretaries of the Constituent Societies. (b) Make arrangements for the Annual Meeting with the Local Committee, with the approval of the Executive Committee. (c) Print in convenient combined form and distribute to the membership of the Federation the programs of the Constituent Societies as received from their respective Secretaries. (d) Undertake such other duties, to be decided upon from time to time by the Executive Committee, as do not conflict with the complete autonomy of the Constituent Societies.

5. The Executive Committee shall control all monies in the hands of the Federation Secretary, who shall make an annual report to the Executive Committee for audit and approval. The expenses of the Federation Secretary, as authorized by the Executive Committee, shall be the first charge on such monies and if insufficient for the purpose the Executive Committee shall prorate such expenses to the Constituent Societies of the Federation in proportion to their respective memberships.

The Executive Committee may appropriate Federation monies annually for the uses of Local Committees and for the uses of other authorized Committees but in the latter cases an audit of expenditures shall be made and approved before such committees are discharged.

6. The Executive Committee shall determine the place of the Annual Meeting, and the time shall be determined by the Local Committee, preferably within the period of March fifteenth to May first.

7. The local Committee at the place of meeting of the Federation shall charge such fee for registration as may be approved by the Executive Committee. The monies thus collected shall be used to defray the expenses of the Local Committee and the remainder, after such expenses have been met, shall be turned over to the Federation Secretary.

8. The Executive Committee shall consider measures of advantage to the Federation as a whole. Any Constituent Society may refer similar measures to the Executive Committee. No action, however, shall be taken by the Executive Committee unless specifically authorized by all the Constituent Societies.

9. The Chairman of the Executive Committee may appoint committees when the purposes of such committees have been approved by all the Constituent Societies of the Federation. Such committees shall be appointed for a term of one year, but may be continued and their members reappointed. Such committees shall report in writing to the Executive Committee, which shall in turn report thereon to the Constituent Societies either for information or recommendation. The Secretaries of the Constituent Societies shall report the recommendations of their respective Societies to the Executive Committee for final action.

10. All individuals whose names appear on the program by invitation or introduction and those registering from any recognized biological laboratory may be enrolled as Associate Members of the Federation for that Annual Meeting. Such Associate Members may enjoy all the privileges of the Annual Meeting except that of voting.

11. No person may present orally more than one paper during all of the scientific sessions of the Constituent Societies at the time of the Annual Meeting except upon invitation of the Executive Committee or a Council. Papers must be submitted to the Secretary of the Society of which the proposer is a member. The proposer may request transfer to another program, but this may only be done with the consent of the Secretary of the Society concerned. Any Secretary who regards any paper submitted to him as better suited to the program of another Society may arrange this transfer with the Secretary of the Society concerned, if it be possible. Such transfer shall be indicated on the program.

12. Abstracts not to exceed two hundred and fifty words in length, of papers approved for presentation at all of the scientific sessions of all the Constituent Societies at the Annual Meeting, shall receive publication in the *Federation Proceedings*.

13. A Control Committee, consisting of at least one representative of each Constituent Society as designated by the several Councils, shall have editorial control over the *Federation Proceedings*

which shall be financed as required by an annual assessment of all the members of each Constituent Society.

14. The Control Committee shall have power to choose certain additional papers presented at the Annual Meetings and from other sources, including material heretofore published in the Federation Yearbook, for publication in the Federation Proceedings.

PLACEMENT SERVICE

The Federation maintains a service to act as a medium of communication between persons seeking positions for teaching or research and institutions that wish to fill vacancies in these sciences.

The service does not undertake to recommend or to pass judgment upon applicants. It aims merely to serve as a clearing-house for such information as above stated and to bring into touch with one another candidates for positions and vacancies to be filled.

Persons, whether members of the Federation or not, and institutions desiring to avail themselves of the service, may receive such information as is available without cost to the applicant.

All communications should be addressed to Dr. H. B. Lewis, Director, University of Michigan, Ann Arbor, Mich.

THE AMERICAN PHYSIOLOGICAL SOCIETY

Founded December 30, 1887; Incorporated June 2, 1923

OFFICERS ELECTED 1942

President—PHILIP BARD, Johns Hopkins School of Medicine, Baltimore, Md.

Secretary—WALLACE O. FENN, University of Rochester, School of Medicine and Dentistry, Rochester, N. Y.

Treasurer—HALLOWELL DAVIS, Harvard University School of Medicine, Boston, Mass.

Council—PHILIP BARD, WALLACE O. FENN, HALLOWELL DAVIS, CHARLES H. BEST, University of Toronto, Canada, MAURICE B. VISSCHER, University of Minnesota, Minneapolis, HIRAM E. ESSEX, Mayo Foundation, Rochester, Minn., W. F. HAMILTON, University of Georgia, Augusta.

Board of Publication Trustees—WALTER J. MEEK, Chairman (1942–45), ANDREW C. IVY (1943–46), HOMER W. SMITH (1944–47).

Representative on the Division of Biology and Agriculture of the National Research Council—MCKEEN CATTELL (1936–1945).

Representative on the Division of Medical Sciences of the National Research Council—H. C. BAZETT (1944–1947).

Representative on the Executive Committee of the Union of American Biological Societies—A. J. CARLSON with C. J. WIGGERS as alternate.

Representative on the Council of the American Association for the Advancement of Science—C. J. WIGGERS with A. SIDNEY HARRIS as alternate.

Historian—WALTER J. MEEK.

PAST OFFICERS

Organization Meeting, December 30, 1887

S. WEIR MITCHELL, *President*
H. N. MARTIN, *Secretary*

1888 H. P. BOWDITCH, President; H. N. MARTIN, Secretary-Treasurer; J. G. CURTIS, H. C. WOOD, H. SEWALL, Councilors. **1889** S. WEIR MITCHELL, President; H. N. MARTIN, Secretary-Treasurer; H. P. BOWDITCH, J. G. CURTIS, H. C. WOODS, Councilors. **1890** S. WEIR MITCHELL, President; H. N. MARTIN, Secretary-Treasurer; H. P. BOWDITCH, J. G. CURTIS, H. H. DONALDSON, Councilors. **1891** H. P. BOWDITCH, President; H. N. MARTIN, Secretary-Treasurer; R. H. CHITTENDEN, J. G. CURTIS, H. N. DONALDSON, Councilors. **1892** H. P. BOWDITCH, President; H. N. MARTIN, Secretary-Treasurer; R. H. CHITTENDEN, J. G. CURTIS, W. H. HOWELL, Councilors. **1893** H. P. BOWDITCH, President; W. P. LOMBARD, Secretary-Treasurer; R. H. CHITTENDEN, J. G. CURTIS, W. H. HOWELL, Councilors. **1894** H. P. BOWDITCH, President; W. P. LOMBARD, Secretary-Treasurer; R. H. CHITTENDEN, W. H. HOWELL, J. W. WARREN, Councilors. **1895** H. P. BOWDITCH, President; F. S. LEE, Secretary-Treasurer; R. H. CHITTENDEN, W. H. HOWELL, W. P. LOMBARD, Councilors. **1896** R. H. CHITTENDEN, President; F. S. LEE, Secretary-Treasurer; H. P. BOWDITCH, W. H. HOWELL, J. W. WARREN, Councilors. **1897** R. H. CHITTENDEN, President; F. S. LEE, Secretary-Treasurer; H. P. BOWDITCH, W. H. HOWELL, W. P. LOMBARD, Councilors. **1898** R. H. CHITTENDEN, President; F. S. LEE, Secretary-Treasurer; H. P. BOWDITCH, W. H. HOWELL, W. P. LOMBARD, Councilors. **1899** R. H. CHITTENDEN, President; F. S. LEE, Secretary-Treasurer; W. H. HOWELL, W. P. LOMBARD, W. T. PORTER, Councilors. **1900** R. H. CHITTENDEN, President; F. S. LEE, Secretary-Treasurer; W. H. HOWELL, W. P. LOMBARD, W. T. PORTER, Councilors. **1901** R. H. CHITTENDEN, President; F. S. LEE, Secretary-Treasurer; W. H. HOWELL, W. P. LOMBARD, W. T. PORTER, Councilors. **1902** R. H. CHITTENDEN, President; F. S. LEE, Secretary-Treasurer; W. H. HOWELL, W. P. LOMBARD, W. T. PORTER, Councilors. **1903** R. H. CHITTENDEN, President; F. S. LEE, Secre-

tary-Treasurer; W. H. HOWELL, W. P. LOMBARD, W. T. PORTER, Councilors. **1904** R. H. CHITTENDEN, President; W. T. PORTER, Secretary-Treasurer; F. S. LEE, W. P. LOMBARD, W. H. HOWELL, Councilors. **1905** W. H. HOWELL, President; L. B. MENDEL, Secretary; W. B. CANNON, Treasurer; R. H. CHITTENDEN, S. J. MELTZER, Councilors. **1906** W. H. HOWELL, President; L. B. MENDEL, Secretary; W. B. CANNON, Treasurer; A. B. MACALLUM, S. J. MELTZER, Councilors. **1907** W. H. HOWELL, President; L. B. MENDEL, Secretary; W. B. CANNON, Treasurer; J. J. ABEL, G. LUSK, Councilors. **1908** W. H. HOWELL, President; R. HUNT, Secretary; W. B. CANNON, Treasurer; J. J. ABEL, G. LUSK, Councilors. **1909** W. H. HOWELL, President; R. HUNT, Secretary; W. B. CANNON, Treasurer; A. J. CARLSON, W. P. LOMBARD, Councilors. **1910** W. H. HOWELL, President; A. J. CARLSON, Secretary; W. B. CANNON, Treasurer; J. ERLANGER, F. S. LEE, Councilors. **1911** S. J. MELTZER, President; A. J. CARLSON, Secretary; W. B. CANNON, Treasurer; J. ERLANGER, F. S. LEE, Councilors. **1912** S. J. MELTZER, President; A. J. CARLSON, Secretary; W. B. CANNON, Treasurer; J. ERLANGER, F. S. LEE, Councilors. **1913** S. J. MELTZER, President; A. J. CARLSON, Secretary; J. ERLANGER, Treasurer; W. B. CANNON, F. S. LEE, Councilors. **1914** W. B. CANNON, President; A. J. CARLSON, Secretary; J. ERLANGER, Treasurer; F. S. LEE, S. J. MELTZER, Councilors. **1915** W. B. CANNON, President; C. W. GREENE, Secretary; J. ERLANGER, Treasurer; W. E. GARREY, W. H. HOWELL, J. J. R. MACLEOD, W. J. MEEK, Councilors. **1916** W. B. CANNON, President; C. W. GREENE, Secretary; J. ERLANGER, Treasurer; W. E. GARREY, W. H. HOWELL, J. J. R. MACLEOD, W. J. MEEK, Councilors. **1917** F. S. LEE, President; C. W. GREENE, Secretary; J. ERLANGER, Treasurer; W. B. CANNON, W. H. HOWELL, J. J. R. MACLEOD, W. J. MEEK, Councilors. **1918** F. S. LEE, President; C. W. GREENE, Secretary; J. ERLANGER, Treasurer; W. B. CANNON, W. H. HOWELL, J. J. R. MACLEOD, W. J. MEEK, Councilors. **1919** W. P. LOMBARD, President; C. W. GREENE, Secretary; J. ERLANGER, Treasurer; W. B. CANNON, Y. HENDERSON, J. J. R. MACLEOD, W. J. MEEK, Councilors. **1920** W. P. LOMBARD, President; C. W. GREENE, Secretary; J. ERLANGER, Treasurer; W. B. CANNON, J. J. R. MACLEOD, Y. HENDERSON, C. J. WIGGERS, Councilors. **1921** J. J. R. MACLEOD, President, C. W. GREENE, Secretary; J. ERLANGER, Treasurer; J. A. E. EYSTER, Y. HENDERSON, C. J. WIGGERS, A. J. CARLSON, Councilors. **1922** J. J. R. MACLEOD, President; C. W. GREENE, Secretary; J. ERLANGER, Treasurer; Y. HENDERSON, C. J. WIGGERS, A. J. CARLSON, J. A. E. EYSTER, Councilors. **1923** A. J. CARLSON, President; C. W. GREENE, Secretary; J. ERLANGER, Treasurer; C. J. WIGGERS, A. B. LUCKHARDT, J. A. E. EYSTER, J. R. MURLIN, Councilors. **1924** A. J. CARLSON, President; W. J. MEEK, Secretary; C. K. DRINKER, Treasurer; A. B. LUCKHARDT, J. A. E. EYSTER, J. R. MURLIN, W. E. GARREY, Councilors. **1925** A. J. CARLSON, President; W. J. MEEK, Secretary; C. K. DRINKER, Treasurer; J. A. E. EYSTER, J. R. MURLIN, W. E. GARREY, JOSEPH ERLANGER, Councilors. **1926** J. ERLANGER, President; W. J. MEEK, Secretary; A. FORBES, Treasurer; J. R. MURLIN, W. E. GARREY, A. B. LUCKHARDT, C. J. WIGGERS, Councilors. **1927** J. ERLANGER, President; W. J. MEEK, Secretary; A. FORBES, Treasurer; W. E. GARREY, A. B. LUCKHARDT, C. J. WIGGERS, R. GESELL, Councilors. **1928** J. ERLANGER, President; W. J. MEEK, Secretary; A. FORBES, Treasurer; A. B. LUCKHARDT, C. J. WIGGERS, R. GESELL, A. J. CARLSON, Councilors. **1929** W. J. MEEK, President; ALFRED C. REDFIELD, Secretary; A. FORBES, Treasurer; C. J. WIGGERS, R. GESELL, A. J. CARLSON, J. R. MURLIN, Councilors. **1930** W. J. MEEK, President; ARNO B. LUCKHARDT, Secretary; A. FORBES, Treasurer; R. GESELL, A. J. CARLSON, J. R. MURLIN, E. G. MARTIN, Councilors. **1931** W. J. MEEK, President; ARNO B. LUCKHARDT, Secretary; ALEXANDER FORBES, Treasurer; A. J. CARLSON, J. R. MURLIN, E. G. MARTIN, JOHN TAIT, Councilors. **1932** ARNO B. LUCKHARDT, President; FRANK C. MANN, Secretary; ALEXANDER FORBES, Treasurer; E. G. MARTIN, W. J. MEEK, J. R. MURLIN, JOHN TAIT, Councilors. **1933** ARNO B. LUCKHARDT, President; FRANK C. MANN, Secretary; ALEXANDER FORBES, Treasurer; HERBERT S. GASSER, ERNEST G. MARTIN, W. J. MEEK, JOHN TAIT, Councilors. **1934** CHARLES W. GREENE, President; FRANK C. MANN, Secretary; ALEXANDER FORBES, Treasurer; HERBERT S. GASSER, ARNO B. LUCKHARDT, W. J. MEEK, JOHN TAIT, Councilors. **1935** FRANK C. MANN, President; ANDREW C. IVY, Secretary; ALEXANDER FORBES, Treasurer; CHARLES H. BEST, HERBERT S. GASSER, ARNO B. LUCKHARDT, W. J. MEEK, Councilors. **1936** FRANK C. MANN, President; ANDREW C. IVY, Secretary; WALLACE O. FENN, Treasurer; CHARLES H. BEST, PHILIP BARD, HERBERT S. GASSER, ARNO B. LUCKHARDT, Councilors. **1937** WALTER E. GARREY, President; ANDREW C. IVY, Secretary; WALLACE O. FENN, Treasurer; CHARLES H. BEST, PHILIP BARD, HERBERT S. GASSER, ARNO B. LUCKHARDT, Councilors. **1938** WILLIAM T. PORTER, Honorary President; WALTER E. GARREY, President; ANDREW C. IVY, Secretary; WALLACE O. FENN, Treasurer; ARNO B. LUCKHARDT, CHARLES H. BEST, PHILIP BARD, HERBERT S. GASSER, Councilors. **1939** ANDREW C. IVY, President; PHILIP BARD, Secretary; WALLACE O. FENN, Treasurer; CHARLES H. BEST, HERBERT S. GASSER, ARNO B. LUCKHARDT, MAURICE B. VISSCHER, Councilors. **1940** ANDREW C. IVY, President; PHILIP BARD, Secretary; CARL J. WIGGERS, Treasurer; CHARLES H. BEST, HERBERT S. GASSER, ARNO B. LUCKHARDT,

MAURICE B. VISSCHER, Councilors. **1941** PHILIP BARD, President; CARL J. WIGGERS, Secretary; HALLOWELL DAVIS, Treasurer; CHARLES H. BEST, ARNO B. LUCKHARDT, MAURICE B. VISSCHER, HIRAM E. ESSEX, Councilors. **1942, 1943** PHILIP BARD, President; WALLACE O. FENN, Secretary; HALLOWELL DAVIS, Treasurer; CHARLES H. BEST, MAURICE B. VISSCHER, HIRAM E. ESSEX, W. F. HAMILTON, Councilors.

CONSTITUTION

I

1. This Society shall be named "THE AMERICAN PHYSIOLOGICAL SOCIETY."

2. The Society is instituted to promote the advance of Physiology and to facilitate personal intercourse between American Physiologists.

II

1. The Society shall consist of ordinary and of honorary members.

2. Any person who has conducted and published original researches in Physiology, and who is a resident of North America, shall be eligible for election as an ordinary member of the Society.

3. Distinguished men of science who have contributed to the advance of Physiology shall be elgible for election as honorary members of the Society. Honorary members shall pay no membership fee. They shall have the right of attending the meetings of the Society, and of taking part in its scientific diseussions, but they shall have no vote.

III

1. The management of the Society shall be vested in a Council consisting of the President, Secretary, Treasurer, and four other members to be chosen from the ordinary members by ballot at each annual meeting. The President, Secretary, and Treasurer shall be elected for one year. The President shall be subject to only one reëlection. The four additional members of the Council shall be elected for a term of four years, and the term of office of one of these councilors shall expire at the close of each annual meeting. He or she shall not be eligible for reëlection for a period of two years.

2. The Council shall have power to fill such vacancies as may occur in its membership or in any committee of the Society unless the vacancy is produced by a resignation presented at a meeting.

IV

1. At least a fortnight before the annual meeting the Secretary shall send to each member a notice of the place and time of each meeting, and shall make such other announcements as the Council shall direct.

2. The annual assessment shall be determined by the Council, and shall be due in advance at the time of the annual meeting. Beyond the ordinary expenditures required by the duties of the Secretary and Treasurer, no money of the Society shall be disbursed save by authority of the Council.

3. Any member whose assessment is two years in arrears shall cease to be a member of the Society, unless at the next annual meeting he shall be reinstated by special vote of the Society; and it shall be the duty of the Treasurer to inform the Secretary that he may notify the said delinquent of his right to appeal to said meeting.

4. Any member who has paid the annual assessment for thirty years, or who has attained the age of sixty-five years, or who has retired because of illness, may be relieved from the payment of the annual assessment.

V

1. The annual meeting of the Society shall be held at a time and place determined by the Council in consultation with the Executive Committee of the Federation of American Societies for Experimental Biology.

2. Special meetings may be held at such times and places as the Council may determine.

VI

1. Proposed changes in the Constitution must be sent in writing to the Secretary at least one month before the date of the meeting at which they are to be considered, and must be signed by at least three ordinary members. The Secretary shall send a printed copy of any proposed change to each ordinary member at least two weeks before the next meeting.

2. If at this meeting two-thirds of the votes cast shall favor the proposed change, it shall be made.

3. At all annual meetings of the Society ten ordinary members shall form a quorum for the transaction of business.

VII

1. The Council may, from the names of the candidates proposed in writing by at least two ordinary members of the Society, nominate candidates for election to ordinary membership. The names of the candidates so nominated, together with the names of their proposers and a statement of their qualifications for membership, shall be posted on a bulletin board at an annual meeting of the Society. The candidates may be balloted for at any session of the same meeting, and one black ball in eight shall exclude.

2. Honorary members shall be proposed by the

Council, and shall be elected by ballot of the members present at an annual meeting and one negative vote in twenty shall exclude.

VIII

If a majority of the Council shall decide that the interests of the Society require the expulsion of a member, the Secretary shall send a notice of this decision to each ordinary member at least two weeks before the next annual meeting. At this meeting the Secretary shall, on behalf of the Council, propose the expulsion; and if two-thirds of the members present vote for it, the member shall be expelled, his assessment for the current year shall be returned to him, and he shall cease to be a member of the Society.

IX

1. The official organs of the Society shall be the *American Journal of Physiology* and such other Journals as the Society shall from time to time establish. These the Society shall own and manage.

2. The management of the *Journals* shall be vested in the Council. The Council shall make a full report to the Society at each annual meeting of the financial condition and the publication policy of the *Journals*.

BY-LAWS

1. All papers read before the Society shall be limited to a length of ten minutes. No person may orally present more than one paper. In case of joint authorship the name of the individual who will orally present the paper shall stand first.

2. Abstracts in duplicate, not to exceed two-hundred and fifty words in length, of all papers to be presented at the Annual Meeting of the Society shall be required by the Secretary for publication in the Federation Proceedings, in accordance with rules approved by the Council.

3. The Council may, upon the request of ten ordinary members, call a special meeting of the Society, at any time and place, for the reading of papers and the promotion of personal intercourse. Such meetings shall be held in accordance with the Constitution and By-Laws of the Society; and if the regular officers of the Society are not present, the members in attendance shall elect a temporary Chairman and Secretary. The latter officer shall forward an account of the scientific proceedings of the meeting to the offical Secretary of the Society for insertion in the minutes; he shall also prepare and transmit to the official Secretary such abstracts of papers read as may be furnished him, and these abstracts shall be published in the *Federation Proceedings* in accordance with By-Law 2.

THE AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, INCORPORATED

Founded December 6, 1906; Incorporated September 12, 1919

OFFICERS ELECTED 1944

President—E. A. Doisy, St. Louis University School of Medicine, St. Louis 4, Mo.

Vice-President—A. B. Hastings, Harvard Medical School, Boston, Mass.

Secretary—A. K. Balls, U. S. Bureau of Agricultural and Industrial Chemistry, Western Regional Research Laboratory, Albany 6, California.

Treasurer—W. C. Stadie, Maloney Clinic, University of Pennsylvania, Philadelphia, Pa.

Councilors-at-large—R. J. Anderson, Sterling Laboratory, Yale University, New Haven, Conn.; H. T. Clarke, Columbia University, New York City; V. du Vigneaud, Cornell University Medical College, New York City 21.

Nominating Committee—H. B. Lewis, Chairman, W. M. Clark, C. F. Cori, H. A. Mattill, W. C. Rose, E. A. Evans, G. O. Burr, C. L. A. Schmidt, J. M. Luck.

PAST OFFICERS

1907 Russell H. Chittenden, President; J. J. Abel, Vice-President; W. J. Gies, Secretary; L. B. Mendel, Treasurer; W. Jones, W. Koch, J. Marshall, T. B. Osborne, Councilors. **1908** John J. Abel, President; Otto Folin, Vice-President; Wm. J. Gies, Secretary; L. B. Mendel, Treasurer; A. B. Macallum, A. P. Mathews, F. G. Novy, Councilors. **1909** Otto Folin, President; T. B. Osborne, Vice-President; Wm. J. Gies, Secretary; L. B. Mendel, Treasurer; J. J. Abel, P. A. Levene, G. Lusk, Councilors. **1910** Thomas B. Osborne, President; L. B. Mendel, Vice-President; A. N. Richards, Secretary; Walter Jones, Treasurer; A. B. Malcallum, A. P. Mathews, V. C. Vaughan, Councilors. **1911** Lafayette B. Mendel, President; A. B. Macallum, Vice-President; A. N. Richards, Secretary; Walter Jones, Treasurer; Wm. J. Gies, A. S. Loevenhart, P. A. Shaffer, Councilors. **1912** Archibald B. Macallum, President; G. Lusk, Vice-President; A. N. Richards, Secretary; Walter Jones, Treasurer; H. P. Armsby, L. B. Mendel, H. G. Wells, Councilors. **1913** Archibald B. Macallum, President; G. Lusk, Vice-President; P. A. Shaffer, Secretary; D. D. Van Slyke, Treasurer; H. P. Armsby, L. B. Mendel,

H. G. Wells, Councilors. **1914** Graham Lusk, President; C. L. Alsberg, Vice-President; P. A. Shaffer, Secretary; D. D. Van Slyke, Treasurer; J. J. Abel, A. B. Macallum, T. B. Osborne, Councilors. **1915** Walter Jones, President; C. L. Alsberg, Vice-President; P. A. Shaeffer, Secretary; D. D. Van Slyke, Treasurer; Otto Folin, G. Lusk, L. B. Mendel, Councilors. **1916** Walter Jones, President; F. P. Underhill, Vice-President; S. R. Benedict, Secretary; D. D. Van Slyke, Treasurer; Otto Folin, A. B. Macallum, P. A. Shaffer, Councilors. **1917** Carl L. Alsberg, President; A. P. Mathews, Vice-President; S. R. Benedict, Secretary; H. C. Bradley, Treasurer; L. J. Henderson, P. A. Shaffer, F. P. Underhill, Councilors. **1918** Carl L. Alsberg, President; A. P. Mathews, Vice-President; S. R. Benedict, Secretary; H. C. Bradley, Treasurer; W. J. Gies, Andrew Hunter, E. V. McCollum, Councilors. **1919** Stanley R. Benedict, President; D. D. Van Slyke, Vice-President; V. C. Myers, Secretary; H. C. Bradley, Treasurer; Andrew Hunter, E. V. McCollum, L. B. Mendel, Councilors. **1920** Stanley R. Benedict, President; D. D. Van Slyke, Vice-President; V. C. Myers, Secretary; H. C. Bradley, Treasurer; Otto Folin, Walter Jones, L. B. Mendel, Councilors. **1921** Donald D. Van Slyke, President; P. A. Shaffer, Vice-President; V. C. Myers, Secretary; H. C. Bradley, Treasurer; S. R. Benedict, Otto Folin, Walter Jones, Councilors. **1922** Donald D. Van Slyke, President; P. A. Shaffer, Vice-President; V. C. Myers, Secretary; W. R. Bloor, Treasurer; S. R. Benedict, H. C. Bradley, A. P. Mathews, Councilors. **1923** Philip A. Shaffer, President; H. C. Sherman, Vice-President; V. C. Myers, Secretary; W. R. Bloor, Treasurer; H. C. Bradley, Andrew Hunter, A. P. Mathews, Councilors. **1924** Philip A. Shaffer, President; Henry C. Sherman, Vice-President; D. Wright Wilson, Secretary; Walter R. Bloor, Treasurer; Otto Folin, Andrew Hunter, Victor C. Myers, Councilors. **1925** Henry C. Sherman, President; Edward C. Kendall, Vice-President; D. Wright Wilson, Secretary; Walter R. Bloor, Treasurer; Otto Folin, Lafayette B. Mendel, Philip A. Shaffer, Councilors. **1926** Edward C. Kendall, President; Elmer V. McCollum, Vice-President; Fred C. Koch, Secretary; Glenn E. Cullen, Treasurer; J. B. Collip, Edward A. Doisy, Albert P. Mathews, Councilors. **1927** E. V. McCollum, President; W. R. Bloor, Vice-President; D. Wright Wilson, Secretary; G. E. Cullen, Treasurer; E. A. Doisy, F. C. Koch, D. D. Van Slyke, Councilors. **1928** E. V. McCollum, President; W. R. Bloor, Vice-President; D. Wright Wilson, Secretary; G. E. Cullen, Treasurer; Wm. M. Clark, F. C. Koch, D. D. Van Slyke, Councilors. **1929** W. R. Bloor, President; H. C. Bradley, Vice-President; H. B. Lewis, Secretary; G. E. Cullen, Treasurer; W. M. Clark, C. L. A. Schmidt, P. A. Shaffer, Councilors. **1930** W. R. Bloor, President; H. C. Bradley, Vice-President; H. B. Lewis, Secretary; G. E. Cullen, Treasurer; W. M. Clark, P. A. Shaffer, D. W. Wilson, Councilors. **1931** H. C. Bradley, President; W. M. Clark, Vice-President; H. B. Lewis, Secretary; C. H. Fiske, Treasurer; W. C. Rose, P. A. Shaffer, D. W. Wilson, Councilors. **1932** H. C. Bradley, President; W. M. Clark, Vice-President; H. B. Lewis, Secretary; C. H. Fiske, Treasurer; P. E. Howe, W. C. Rose, D. W. Wilson, Councilors. **1933** W. M. Clark, President; H. B. Lewis, Vice-President; H. A. Mattill, Secretary; C. H. Fiske, Treasurer; H. C. Bradley, P. E. Howe, W. C. Rose, Councilors. **1934** W. M. Clark, President; H. B. Lewis, Vice-President; H. A. Mattill, Secretary; C. H. Fiske, Treasurer; H. C. Bradley, E. A. Doisy, P. E. Howe, Councilors. **1935** H. B. Lewis, President; G. E. Cullen, Vice-President; H. A. Mattill, Secretary; C. H. Fiske, Treasurer; H. C. Bradley, J. B. Collip, E. A. Doisy, Councilors. **1936** H. B. Lewis, President; G. E. Cullen, Vice-President; H. A. Mattill, Secretary; A. B. Hastings, Treasurer; J. B. Collip, E. A. Doisy, W. C. Rose, Councilors. **1937** G. E. Cullen, President; W. C. Rose, Vice-President; H. A. Mattill, Secretary; A. B. Hastings, Treasurer; E. A. Doisy, H. B. Lewis, H. B. Vickery, Councilors. **1938** G. E. Cullen, President; W. C. Rose, Vice-President; Charles G. King, Secretary; A. B. Hastings, Treasurer; H. B. Lewis, H. A. Mattill, H. B. Vickery, Councilors. **1939** W. C. Rose, President; R. J. Anderson, Vice-President; Charles G. King, Secretary; A. B. Hastings, Treasurer; H. B. Lewis, H. A. Mattill, G. E. Cullen, Councilors. **1940** William C. Rose, President; Rudolph J. Anderson, Vice-President; Charles G. King, Secretary; A. B. Hastings, Treasurer; H. A. Mattill, Glenn E. Cullen, E. A. Doisy, Councilors. **1941** R. J. Anderson, President; E. A. Doisy, Vice-President; A. K. Balls, Secretary; W. C. Stadie, Treasurer; H. B. Lewis, W. C. Rose, Councilors. **1942** R. J. Anderson, President; E. A. Doisy, Vice-President; A. K. Balls, Secretary; W. C. Stadie, Treasurer; W. C. Rose, C. A. King, H. Y. Clarke, Councilors. **1943** E. A. Doisy, President; A. B. Hastings, Vice-President; A. K. Balls, Secretary; W. C. Stadie, Treasurer; W. C. Rose, H. T. Clarke, R. J. Anderson, Councilors.

CONSTITUTION

From the Articles of Incorporation

1. The name of the proposed corporation is "American Society of Biological Chemists, Incorporated."

2. The purposes for which this corporation is formed are to further the extension of biochemical knowledge and to facilitate personal intercourse between American investigators in biological chemistry.

BY-LAWS

Article I.—*Membership*

Section 1. *Eligibility for Membership.*—Qualified investigators who have conducted and published meritorious original investigations in biological chemistry shall be eligible for membership in the Society.

Sec. 2. *Nomination.*—Nominations for membership shall be made and seconded by members of the Society on blanks furnished by the Secretary. Nominations shall be submitted to the Council who shall determine eligibility and make recommendation to the Society at a regular meeting.

Sec. 3. *Election to Membership.*—A. A nominee for membership may be voted for by ballot at any meeting of the Society after Council has reported its findings on his eligibility. The eligible candidate shall be reported by the Council as "eligible" or as "eligible and indorsed." B. A majority of the ballots cast shall elect.

Sec. 4. *Forfeiture.*—A. Any member who may grant the use of his name for (a) the advertisement of a patent medicine, a proprietary food preparation, or any other commercial article of doubtful value to the public or possibly harmful to the public health, or (b) who may concede its use for the purpose of encouraging the sale of individual samples (of any such product) that he has not examined, shall forfeit his membership.

B. The Council shall have authority to announce forfeiture of membership, provided that the copy of the charges, together with a written notice of a hearing thereon by the Council at a place and time specified in such notice, shall have been delivered to the member charged with violating the preceding section either personally or mailed to him at his last known address at least thirty days before the date of such hearing.

Sec. 5. *Expulsion.*—Upon the recommendation of the Council any member may be expelled by a majority vote of the total membership at a meeting of the Society, provided that a copy of the charges against him, together with a written notice of a hearing thereon by the Council at a place and time specified in such notice shall have been delivered to him personally or mailed to him at his last known address at least thirty days before the date of such hearing.

Article II.—*Meetings and Quorum*

Section 1. *Annual.*—The annual meeting of the Society shall be held on the date fixed by the Certificate of Incorporation.

Sec. 2. *Special.*—A special meeting may be called at any time by the President, or in case of his absence or disability, by the Vice-President, and must be called at the request of a majority of the Council or fifteen members of the Society. A notice specifying the purpose of such meeting shall be mailed to each member at least ten days previous thereto. The Council shall select the places at which meetings shall be held.

Sec. 3. *Quorum.*—Fifteen members shall constitute a quorum at all meetings of the Society, but in absence of a quorum any number shall be sufficient to adjourn to a fixed date.

Article III.—*Officials*

Section 1. *Officers.*—The officers shall be a President, a Vice-President, a Secretary, and a Treasurer, who shall be elected annually by the members of the Society.

Sec. 2. *Council.*—A. The officers so elected and three additional members, one of whom shall be elected at each annual meeting of the Society to serve a three year term, shall constitute the Board of Directors of the corportion and shall be known as "The Council." (When this provision is first put into effect three members will need to be elected for a one, a two and a three year period.)

B. No two members of the Council may be from the same institution, and none of the officers so elected shall be eligible for re-election for more than two years except the Secretary and Treasurer, who shall be eligible for re-election for five years. The three additional members of the Council shall be ineligible for re-election (until after the lapse of one year).

Sec. 3. *Duties of Officers.*—The powers and duties of the officers elected by the Society shall be such as usually devolve upon their respective positions.

Sec. 4. *Assistant Treasurer.*—A. The Council may from time to time appoint a trust company, or some member of the Society, to serve during the pleasure of the Council as Assistant Treasurer, and to act as depositary of the investments and income of the "Christian A. Herter Memorial Fund" and of such other funds as the Society may from time to time commit to its or his charge.

B. The Assistant Treasurer shall have and exercise the following powers and duties, viz., the custody and safe-keeping of securities and cash belonging to the "Christian A. Herter Fund" and the collection of income and other moneys due to

the Fund, with power to receipt for the same an to endorse for deposit all checks payable to the Society or the Treasurer, or to the Journal of Biological Chemistry for income or other moneys due to the Fund, the investment or reinvestment of the capital of the Fund, subject to the approval of the Council; the dibursement of principal under the direction of the Council and the disbursement of income under the direction of the Editorial Board of the Journal of Biological Chemistry, such disbursement to be made under a resolution of the Council or Board, or with the approval of two members of either the Council or Board, as the case may be. The Assistant Treasurer shall keep books of account and render statements, annually or oftener upon the request of the Council or Board setting forth the condition of the Fund and the receipts and disbursements since the date of the preceding statement.

Article IV.—*The Council*

Section 1. *Powers.*—The general management of the Society during the intervals between meetings shall be vested in the Council, which shall regularly perform the ordinary duties of an executive committee and possess all the powers conferred upon the Board of Directors of a membership corporation by the Membership Corporation Law of the State of New York.

Sec. 2. *Reports.*—The Council shall report to the Society as promptly as possible its findings on the eligibility of candidates for membership, and on all charges of a violation of these By-Laws.

Sec. 3. *Journal of Biological Chemistry.*—The Council shall have power to appoint the persons to act as proxies for the Society at all meetings of the stockholders of the "Journal of Biological Chemistry" (a corporation) of which all the stock is owned by the Society, and also to designate the persons to be elected as Directors of such corporation.

Sec. 4. *Herter Fund.*—It shall be the duty of the Council to see that the "Christian A. Herter Memorial Fund" is administered in accordance with the terms of the Trust Agreement, dated May 16, 1911, executed by the Journal of Biological Chemistry and the donors of said Fund.

Article V.—*Nominating Committee*

Section 1, *Membership.*—A. The nominating Committee shall consist of nine members from nine different institutions elected at each annual meeting to serve for the ensuing year. Members who have served on the Nominating Committee for two consecutive years shall be ineligible for re-election until after the lapse of one year.

B. The member of the Nominating Committee who is elected to the Committee by the largest number of votes shall become Chairman and Secretary of the Committee.

Sec. 2. *Nomination of Officials.*—A. The Nominating Committee shall make at least one nomination for each of the four offices and for each of the three additional positions in the Council to be filled by vote of the members.

B. The nominations by the Nominating Committee must be transmitted to the Secretary at least one month before the annual meeting at which they are to be considered.

C. The Secretary shall send to every member, at least two weeks before the annual meeting, two copies of the list of nominees presented to him by the Nominating Committee and at the same time shall notify all the members that they may vote by proxy.

D. At the opening of the first executive session of the ensuing annual meeting the Secretary shall formally present the regular nominations for the Nominating Committee.

E. Additional nominations for the offices and for membership in the Council may be made by any member at the opening of the first executive session of any annual meeting.

F. Nominations for membership on the Nominating Committee shall be made by or for individual members, either in person or by proxy, and not otherwise, at the opening of the first executive session of any annual meeting.

Sec. 3. *Election of Officials.*—A. The Secretary shall receive and present to the tellers, appointed by the President to take charge of the election, all signed ballots forwarded by absent members. When such ballots are presented to the tellers the Secretary shall announce the names of the members voting by proxy, and he shall record the same names in the minutes of the meeting.

B. All elective officials shall be selected by ballot at the close of the first executive session of each annual meeting.

C. A majority of the votes cast shall be necessary to elect an official.

D. Elective officials shall take office on July 1st following the annual meeting.

Sec. 4. *Filling of Vacancies.*—A. The Nominating Committee shall fill all vacancies in elective positions except such as may occur at a meeting of the Society.

B. The President of the Society shall fill all vacancies in appointive positions.

Article VI.—*Financial*

Section 1. *Dues.*—Annual assessments shall be determined by majority vote at the annual meetings, upon the recommendation of the Council, and shall be due January 15th in each year. Members who have reached the age of 65 years, or who have become incapacitated, may, by vote of the Council, be exempted from the payment of dues.

SEC. 2. *Expenditures.*—No expenditures from the general funds of the Society except those required in the performance of the ordinary official duties shall be made except by vote of the Society or the Council, but this section shall not apply to expenditures from the "Christian A. Herter Memorial Fund."

SEC. 3. *Privileges of Membership Begin with Payment of Dues.*—Candidates for membership, if elected, shall not be entitled to any of the privileges of membership, before they pay the dues of the fiscal year succeeding their election.

SEC. 4. *Penalty for Non-Payment of Dues.*—A. Members in arrears for dues for a period of three consecutive years shall thereupon forfeit their membership.

B. Delinquent members may be reinstated by the Council provided all indebtedness to the Society is liquidated.

SEC. 5. *Herter Fund.*—The "Christian A. Herter Memorial Fund" shall be held and invested separately from the general funds of the Society and the income thereof shall be expended under the direction of the Editorial Board exclusively for the maintenance and support of the Journal of Biological Chemistry, subject to the supervision and control of the Editorial Committee in accordance with the terms of the Trust Agreement mentioned in ARTICLE IV, SECTION 4, and the provisions of ARTICLE VII of the By-Laws.

ARTICLE VII.—*Journal of Biological Chemistry*

SECTION 1. *Editorial Committee.*—There shall be an Editorial Committee consisting of nine members of the Society who shall be nominated by the Nominating Committee and elected by the Society in the same manner as officers. The nine members first elected shall divide themselves by lot into three classes of three in each class, to serve for two, four, and six years respectively, and thereafter three members shall be elected at each alternate annual meeting of the Society to succeed the members of the outgoing class and to serve for a term of six years. Members of the Committee shall be eligible to re-election.

SEC. 2. *Powers of Committee.*—The Committee shall have power to elect an Editorial Board and shall have final authority in matters pertaining to the general policy of the Journal.

SEC. 3. *Editorial Board.*—The members of the Board shall hold office until their successors are elected and shall appoint a Managing Editor from among their own number who shall have direct responsibility and authority for the active editorial conduct of the Journal, and who shall have discretionary power in arranging the details as to the conduct of the Journal. The expenditures of the income of the "Christian A. Herter Memorial Fund" shall be under the direction of the Board, and the approval of any two members of the Board shall be a sufficient warrant to authorize payments from such income.

ARTICLE VIII.—*Papers on Scientific Subjects*

SECTION 1. *Presentation of Papers.*—The Secretary shall request each member who signifies his intention of reading a paper at any session to specify the length of time which its presentation will require. The time thus specified shall be printed on the official program, and the presiding officer shall have no authority to extend it unless a majority of the members present signify their wish to the contrary. In the absence of any specification of time required not more than ten minutes shall be allotted for the reading of any one paper.

SEC. 2. *Number of Papers.*—No member shall be permitted to present more than one paper, either alone or in collaboration, until every member shall have had the opportunity of presenting one paper.

ARTICLE IX.—*Corporate Seal*

SECTION 1. The corporate seal of the corporation shall be a circle surrounded by the words, "AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS," and including the word, "INCORPORATED."

ARTICLE X.—*Amendments*

SECTION 1. *Amendments.*—These By-Laws, after having been approved by the Council, and adopted by the Society at its first annual meeting, shall not be amended except as hereinafter provided.

SEC. 2. *Manner of Presentation.*—Proposed amendments to the By-Laws must be sent to the Secretary at least one month before the date of the meeting at which they are to be considered and must be indorsed in writing by at least three members.

SEC. 3. *Notice of Intended Amendments.*—The Secretary shall give every member notice of proposed amendments at least two weeks before the meeting at which they are to be considered and shall notify all members that they may vote by proxy.

SEC. 4. *Adoption of Amendments.*—A. The Secretary shall receive and present to the tellers appointed by the President all signed ballots forwarded by absent members. When such ballots are presented to the tellers, the Secretary shall announce the names of members voting by proxy, and he shall record the same names in the minutes of the meeting.

B. Votes upon amendments shall be cast at the opening of the second executive session of the meeting at which they are considered.

C. Affirmative votes from three-fifths of the members voting shall be required for the adoption of an amendment.

AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, INCORPORATED

Founded December 28, 1908; Incorporated June 19, 1933

OFFICERS ELECTED 1944

President—ERWIN E. NELSON, Wellcome Research Laboratories, Tuckahoe 7, New York.

Vice-President—CHARLES M. GRUBER, Jefferson Medical College, Philadelphia 7, Pennsylvania.

Secretary—RAYMOND N. BIETER, University of Minnesota Medical School, Minneapolis 14, Minnesota.

Treasurer—McKEEN CATTELL, Cornell University Medical College, New York 21, New York.

Council—HARRY BECKMAN, Marquette University School of Medicine, Milwaukee 3, Wisconsin, NATHAN B. EDDY, National Institute of Health, Bethesda 14, Maryland, ERWIN E. NELSON, CHARLES M. GRUBER, RAYMOND N. BIETER, McKEEN CATTELL.

Membership Committee—HARVEY B. HAAG (term expires 1945), Medical College of Virginia, Richmond 19, Virginia, CARL A. DRAGSTEDT (term expires 1946) Northwestern University Medical School, Chicago 11, Ill., CARL F. SCHMIDT (term expires 1947), University of Pennsylvania Medical School, Philadelphia 4, Pennsylvania.

Nominating Committee—H. O. CALVERY, Chairman, A. C. DEGRAFF, J. M. DILLE, B. H. ROBBINS, F. F. YONKMAN.

PAST OFFICERS

1909 J. J. ABEL, President; REID HUNT, Secretary; A. S. LOEVENHART, Treasurer; S. J. MELTZER, T. SOLLMANN, C. W. EDMUNDS, A. C. CRAWFORD, Councilors. **1910** J. J. ABEL, President; REID HUNT, Secretary; A. S. LOEVENHART, Treasurer; A. C. CRAWFORD, G. B. WALLACE, Councilors. **1911** J. J. ABEL, President; REID HUNT, Secretary; A. S. LOEVENHART, Treasurer; G. B. WALLACE, W. DEB. MACNIDER, Councilors. **1912** J. J. ABEL, President; J. AUER, Secretary; A. S. LOEVENHART, Treasurer; G. B. WALLACE, REID HUNT, Councilors. **1913** T. SOLLMANN, President; J. AUER, Secretary; A. S. LOEVENHART, Treasurer; J. J. ABEL, W. DEB. MACNIDER, councilors. **1914** T. SOLLMANN, President, J. AUER, Secretary; W. DEB. MACNIDER, Treasurer; J. J. ABEL, A. S. LOEVENHART, Councilors. **1915** T. SOLLMANN, President; J. AUER, Secretary; W. DEB. MACNIDER, Treasurer; WORTH HALE, D. E. JACKSON, Councilors. **1916** REID HUNT, President; J. AUER, Secretary; W. DEB. MACNIDER, Treasurer; A. D. HIRSCHFELDER, G. B. ROTH, Councilors. **1917** REID HUNT, President; L. G. ROWNTREE, Secretary; W. DEB. MACNIDER, Treasurer; J. AUER, CARL VOEGTLIN, Councilors. **1918** REID HUNT, President; E. D. BROWN, Secretary; W. DEB. MACNIDER, Treasurer; HUGH McGUIGAN, CARL VOEGTLIN, Councilors. **1919** A. S. LOEVENHART, President; E. D. BROWN, Secretary; W. DEB. MACNIDER, Treasurer; REID HUNT, E. K. MARSHALL, JR., Councilors. **1920** A. S. LOEVENHART, President; E. D. BROWN, Secretary; W. DEB. MACNIDER, Treasurer; D. E. JACKSON, E. K. MARSHALL, JR., Councilors. **1921** C. W. EDMUNDS, President; E. D. BROWN, Secretary; HUGH McGUIGAN, Treasurer; JOHN AUER, J. P. HANZLIK, Councilors. **1922** C. W. EDMUNDS, President; E. D. BROWN, Secretary; HUGH McGUIGAN, Treasurer; J. P. HANZLIK, H. G. BARBOUR, Councilors. **1923** C. W. EDMUNDS, President; E. D. BROWN, Secretary; HUGH McGUIGAN, Treasurer; J. P. HANZLIK, H. G. BARBOUR, Councilors. **1924** JOHN AUER, President; E. D. BROWN, Secretary; A. L. TATUM, Treasurer; J. P. HANZLIK, H. G. BARBOUR, Councilors. **1925** JOHN AUER, President; E. D. BROWN, Secretary; A. L. TATUM, Treasurer; H. G. BARBOUR, W. DEB. MACNIDER, Councilors. **1926** JOHN AUER, President; E. D. BROWN, Secretary; A. L. TATUM, Treasurer; H. G. BARBOUR, W. DEB. MACNIDER, Councilors. **1927** CARL VOEGTLIN, President; E. D. BROWN, Secretary; A. L. TATUM, Treasurer; V. E. HENDERSON, C. W. EDMUNDS, Councilors. **1928** CARL VOEGTLIN, President; E. D. BROWN, Secretary; A. L. TATUM, Treasurer; V. E. HENDERSON, C. W. EDMUNDS, Councilors. **1929** CARL VOEGTLIN, President; E. D. BROWN, Secretary; O. H. PLANT, Treasurer; V. E. HENDERSON, C. W. EDMUNDS, Councilors. **1930** GEORGE B. WALLACE, President; E. D. BROWN, Secretary; O. H. PLANT, Treasurer; H. G. BARBOUR, C. M. GRUBER, Councilors. **1931** GEORGE B. WALLACE, President; VELYIEN E. HENDERSON, Secretary; O. H. PLANT, Treasurer; PAUL D. LAMSON, WILLIAM DEB. MACNIDER, Councilors. **1932** WM. DEB. MACNIDER, President; A. N. RICHARDS, Vice-President; V. E. HENDERSON, Secretary; O. H. PLANT, Treasurer; G. B. ROTH, A. L. TATUM, Councilors. **1933** WM. DEB. MACNIDER, President; A. L. TATUM, Vice-President; V. E. HENDERSON, Secretary; O. H. PLANT, Treasurer; C. M. GRUBER, G. B. ROTH, Councilors. **1934** R. A. HATCHER, President; A. L. TATUM, Vice-President; E. M. K. GEILING, Secretary; O. H. PLANT, Treasurer; WM. DEB. MACNIDER, R. L. STEHLE, Councilors. **1935** V. E. HENDERSON, President; O. H. PLANT, Vice-President; E. M. K. GEILING, Secretary; C. M. GRUBER, Treasurer; FLOYD DE EDS, M. S. DOOLEY, Councilors. **1936** V. E. HENDERSON, Presi-

dent; O. H. PLANT, Vice-President; E. M. K. GEILING, Secretary; C. M. GRUBER, Treasurer; C. W. EDMUNDS, G. B. WALLACE, Councilors. **1937** A. L. TATUM, President; E. M. K. GEILING, Vice-President; G. P. GRABFIELD, Secretary; C. M. GRUBER, Treasurer; V. E. HENDERSON, M. H. SEEVERS, Councilors. **1938** A. L. TATUM, President; E. M. K. GEILING, Vice-President; G. P. GRABFIELD, Secretary; C. M. GRUBER, Treasurer; E. K. MARSHALL, JR., C. F. SCHMIDT, Councilors. **1939** O. H. PLANT, President; E. M. K. GEILING, Vice-President; G. P. GRABFIELD, Secretary; E. E. NELSON, Treasurer; A. L. TATUM, C. A. DRAGSTEDT, Councilors. **1940** E. M. K. GEILING, President; C. F. SCHMIDT, Vice-President; G. PHILIP GRABFIELD, Secretary; E. E. NELSON, Treasurer; B. H. ROBBINS, C. H. THIENES, Councilors **1941** E. M. K. GEILING, President; C. F. SCHMIDT, Vice-President; RAYMOND N. BIETER, Secretary; E. E. NELSON, Treasurer; E. G. GROSS, R. G. SMITH, Councilors. **1942** E. K. MARSHALL, JR., President; CARL A. DRAGSTEDT, Vice-President; RAYMOND N. BIETER, Secretary; E. E. NELSON, Treasurer; MCK. CATTELL, R. G. SMITH, Councilors. **1943** E. K. MARSHALL, JR., President; CARL A. DRAGSTEDT, Vice-President; RAYMOND N. BIETER, Secretary; E. E. NELSON, Treasurer; MCK. CATTELL, R. G. SMITH, Councilors.

CONSTITUTION

ARTICLE I.—*Name*

The name of this organization shall be the "AMERICAN SOCIETY FOR PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, INCORPORATED."

ARTICLE II.—*Objects*

The purpose of this Society shall be to promote these branches of science and to facilitate personal intercourse between investigators who are actively engaged in research in these fields.

ARTICLE III.—*Membership*

SECTION 1. Any person who has conducted and published a meritorious investigation in pharmacology or experimental therapeutics, and who is an active investigator in one of these fields, shall be eligible to membership, subject to the conditions of the other sections of Article III.

SEC. 2. A. Candidates for membership to this Society shall be proposed by two members who are not members of the Council. The names so proposed shall be sent to the Secretary at least three months prior to the Annual Meeting.

B. The Membership Committee shall investigate the qualifications of the candidates and report to the Council.

C. Candidates reported upon by the Membership Committee to the Council may be recommended for admission by the Council only provided they have been unanimously approved by both the Membership Committee and the Council.

D. The names of the candidates recommended for admission by the Council shall be posted by the Secretary not later than the day preceding the election for members.

E. The election of members shall be by individual ballot; one opposing vote in every eight cast shall be sufficient to exclude a candidate from membership.

SEC. 3. *Forfeiture of Membership.*

A. Any member whose assessment is three years in arrears shall cease to be a member of the Society, unless he shall be reinstated by a special vote of the Council; and it shall be the duty of the Treasurer to inform the Secretary that he may notify the said delinquent of his right to appeal to the Council.

B. If the Council shall decide that it is for the best interests of the Society that a member be expelled, the member shall be notified and given an opportunity of a hearing before the Council. Upon the recommendation of the Council the member then may be expelled by a three-fourths vote of those present at a regular meeting of the Society.

SEC. 4. *Honorary Members.*

A. Distinguished men of science who have contributed to the advance of pharmacology or experimental therapeutics shall be eligible for election as honorary members of the Society.

B. Nominations for honorary members shall take the same course as nominations for ordinary members (Art. III, Sec. 2); but their election shall require the unanimous vote of the members present at the election.

C. Honorary members shall pay no membership fee. They shall have the right to attend all meetings of the Society, and to take part in its discussions, but they shall have no vote.

D. The conditions for continuation of membership shall be the same for honorary as for ordinary members (Art. III, Sec. 3), except that forfeiture for arrears of fees does not apply to honorary members.

ARTICLE IV.—*Officers and Elections*

SECTION 1. The management of the Society shall be vested in a Council of six officers, consisting of a President, a Vice-President, a Secretary, a Treasurer, and two additional members.

SEC. 2. There shall be a Membership Committee consisting of three members, and a Nominating Committee consisting of five members. No two members of either Committee shall be from the same institution.

SEC. 3. Members of the Council shall serve for one year but they shall be eligible for re-election.

SEC. 4. The election of the Membership Committee shall be held annually at the time when the election of officers occurs. At the first meeting of the Society under this Constitution, one member shall be elected to serve on the Committee for three years, one for two years, and one for one year; and subsequently one member shall be elected each year to serve for a period of three years.

SEC. 5. A. Members of the Nominating Committee shall serve for one year. They are eligible for re-election, but shall not hold membership in the Committee for more than two consecutive years.

B. The Nominating Committee shall make at least one nomination for each office and for position on the Membership Committee to be filled by vote of the members. The nominations so made shall be transmitted to the Secretary and by him in turn to the members, at least one month before the annual meeting. Additional nominations may be made by any member at the time of the annual meeting.

C. Nominations for membership on the Nominating Committee shall be made by individual members at the time of the annual election. The five nominees who receive the highest number of votes shall be declared elected. The Nominating Committee shall select its own chairman who shall also serve as secretary to the Committee.

SEC. 6. The election of officers shall be held at the close of the first session of the annual meeting. In voting there shall be a ballot in regular order for each office to be filled, and the majority of the votes cast shall be necessary to a choice.

SEC. 7. Such vacancies as may occur in the offices and in the various committees in the interval between annual meetings shall be filled by a majority vote of the Council.

ARTICLE V.—*Meetings*

SECTION 1. The annual meeting of the Society shall be held at a time and place determined by the Council in consultation with the Executive Committee of the Federation of American Societies for Experimental Biology.

SEC. 2. Special meetings may be held at such times and places as the Council may determine.

SEC. 3. At least four weeks before the annual meeting the Secretary shall send to each member a notice of the time and place of such meeting and shall make such announcements as the Council may direct.

ARTICLE VI.—*Financial*

SECTION 1. The annual assessment shall be determined by majority vote at the annual meetings, upon the recommendation of the Council, and shall be due in advance at the time of the meeting.

SEC. 2. Beyond the ordinary expenditures required by the routine business of the Society no money shall be disbursed save by the authority of the Council or Society.

SEC. 3. The treasurer shall make an annual report to the Society.

SEC. 4. In case any profits result to the Society from the Journal of Pharmacology and Experimental Therapeutics at the end of the financial year, such profits shall be kept in a special account, after deducting any sums expended by the Society during the year for the conduct of the Journal, and shall be held subject to the order of the Council on recommendation of the Editorial Board.

ARTICLE VII.—*Quorum*

Ten members shall constitute a quorum for the transaction of business.

ARTICLE VIII.—*By-Laws*

By-Laws shall be adopted, altered or repealed at any meeting by two-thirds vote of the ballots cast.

ARTICLE IX.—*Amendments*

SECTION 1. Intended amendments to the Constitution shall be sent to the Secretary at least one month before the date of the meeting at which they are to be considered, and must be indorsed in writing by at least three members.

SEC. 2. The Secretary shall give all members due notice of proposed amendments.

SEC. 3. A four-fifths vote of the members present shall be required for the adoption of an amendment.

ARTICLE X.—*Journal*

SECTION 1. The official publication of the Society shall be the Journal of Pharmacology and Experimental Therapeutics.

SEC. 2. The Society shall elect an Editor-in-Chief for a term of three years and he with the approval approval of the Council shall appoint an Editorial Board of six members for a term of three years.

SEC. 3. The Editorial Board shall have direct authority and responsibility for the active editorial conduct of the Journal of Pharmacology and Experimental Therapeutics and shall have discretionary power in arranging details as to the conduct of the Journal.

BY-LAWS

1. Papers to be read shall be selected by the President and Secretary, who shall be empowered to arrange the program in their discretion. Papers

not read shall appear on the program as read by title. No member shall be permitted to read or have read by title more than one paper.

2. An abstract of a paper to be read before the Society shall be sent to the Secretary with the title. As early as possible after each meeting, the Secretary shall edit and publish the Proceedings of the Society together with abstracts in a publication authorized by the Society.

3. All applications for membership shall be accompanied by a copy of as many reprints as possible of the published work of the applicant.

THE AMERICAN SOCIETY FOR EXPERIMENTAL PATHOLOGY

Founded December 29, 1913

OFFICERS ELECTED 1942

President—BALDUIN LUCKÉ, University of Pennsylvania Medical School, Philadelphia.

Vice-President—PAUL R. CANNON, University of Chicago, Chicago, Illinois.

Secretary-Treasurer—H. P. SMITH, College of Medicine, State University of Iowa, Iowa City.

Councilors—DOUGLAS H. SPRUNT, University of Tennessee, Memphis, FRIEDA S. ROBSCHEIT-ROBBINS, University of Rochester School of Medicine and Dentistry, Rochester, N. Y.

PAST OFFICERS

1914 R. M. PEARCE, President; JOHN F. ANDERSON, Vice-President; G. H. WHIPPLE, Secretary-Treasurer; HARVEY CUSHING, DAVID MARINE, Councilors. **1915** THEOBALD SMITH, President; G. H. WHIPPLE, Vice-President; PEYTON ROUS, Secretary-Treasurer; DAVID MARINE, R. M. PEARCE, Councilors. **1916** SIMON FLEXNER, President; LEO LOEB, Vice-President; PEYTON ROUS, Secretary-Treasurer; DAVID MARINE, R. M. PEARCE, Councilors. **1917** LUDVIG HEKTOEN, President; LEO LOEB, Vice-President; HOWARD T. KARSNER, Secretary-Treasurer; PAUL A. LEWIS, L. G. ROWNTREE, Councilors. **1918** H. GIDEON WELLS, President; W. G. MACCALLUM—Vice-President; HOWARD T. KARSNER, Secretary-Treasurer; L. G. ROWNTREE, LUDVIG HEKTOEN, Councilors. **1919** W. G. MACCALLUM, President; WILLIAM H. PARK, Vice-President; HOWARD T. KARSNER, Secretary-Treasurer; LUDVIG HEKTOEN, E. L. OPIE, Councilors. **1920** WILLIAM H. PARK, President; F. G. NOVY, Vice-President; HOWARD T. KARSNER, Secretary-Treasurer; E. L. OPIE, WADE H. BROWN, Councilors. **1921** F. G. NOVY, President; HOWARD T. KARSNER, Vice-President; WADE H. BROWN, Secretary-Treasurer; PAUL A. LEWIS, A. R. DOCHEZ, Councilors. **1922** HOWARD T. KARSNER, President; EUGENE L. OPIE, Vice-President; WADE H. BROWN, Secretary-Treasurer; A. R. DOCHEZ, GEORGE H. WHIPPLE, Councilors. **1923** EUGENE L. OPIE, President; ALDRED S. WARTHIN, Vice-President; WADE H. BROWN, Secretary-Treasurer; GEORGE H. WHIPPLE, H. GIDEON WELLS, Councilors. **1924** ALDRED S. WARTHIN, President; GEORGE H. WHIPPLE, Vice-President; EDWARD B. KRUMBHAAR, Secretary-Treasurer; H. GIDEON WELLS, FREDERICK L. GATES, Councilors. **1925** GEORGE H. WHIPPLE, President; WADE H. BROWN, Vice-President; EDWARD B. KRUMBHAAR, Secretary-Treasurer; FREDERICK L. GATES, DAVID MARINE, Councilors. **1926** WADE H. BROWN, President; DAVID MARINE, Vice-President; EDWARD B. KRUMBHAAR, Secretary-Treasurer; FREDERICK L. GATES, WILLIAM F. PETERSEN, Councilors. **1927** DAVID MARINE, President; EDWARD B. KRUMBHAAR, Vice-President; CARL V. WELLER, Secretary-Treasurer; WILLIAM F. PETERSEN, FREDERICK L. GATES, Councilors. **1928** EDWARD B. KRUMBHAAR, President; WILLIAM F. PETERSEN, Vice-President; CARL V. WELLER, Secretary-Treasurer; FREDERICK L. GATES, SAMUEL R. HAYTHORN, Councilors. **1929** WILLIAM F. PETERSEN, President; FREDERICK L. GATES, Vice-President; CARL V. WELLER, Secretary-Treasurer; SAMUEL R. HAYTHORN, PEYTON ROUS, Councilors. **1930** FREDERICK L. GATES, President; SAMUEL R. HAYTHORN, Vice-President; C. PHILLIP MILLER, Secretary-Treasurer; PEYTON ROUS, CARL V. WELLER, Councilors. **1931** SAMUEL R. HAYTHORN, President; PEYTON ROUS, Vice-President; C. PHILLIP MILLER, Secretary-Treasurer; CARL V. WELLER, S. BURT WOLBACH, Councilors. **1932** PEYTON ROUS, President; CARL V. WELLER, Vice-President; C. PHILLIP MILLER, Secretary-Treasurer; S. BURT WOLBACH, OSKAR KLOTZ, Councilors. **1933** CARL V. WELLER, President; S. BURT WOLBACH, Vice-President; C. PHILLIP MILLER, Secretary-Treasurer; OSKAR KLOTZ, ALPHONSE R. DOCHEZ, Councilors. **1934** S. BURT WOLBACH, President; OSKAR KLOTZ, Vice-President; SHIELDS WARREN, Secretary-Treasurer; C. PHILLIP MILLER, ALPHONSE R. DOCHEZ, Councilors. **1935** OSKAR KLOTZ, President; ALPHONSE R. DOCHEZ, Vice-President; SHIELDS WARREN, Secretary-Treasurer; MORTON MCCUTCHEON, C. PHILLIP MILLER, Councilors. **1936** ALPHONSE R. DOCHEZ, President; C. PHILLIP MILLER, Vice-President; SHIELDS WARREN, Secretary-Treasurer; MORTON

McCutcheon, Ernest W. Goodpasture, Councilors. **1937** C. Phillip Miller, President; Morton McCutcheon, Vice-President; Paul R. Cannon, Secretary-Treasurer; Eenest W. Goodpasture, Shields Warren, Councilors. **1938** Morton McCutcheon, President; Ernest W. Goodpasture, Vice-President; Paul R. Cannon, Secretary-Treasurer; Shields Warren, Jesse L. Bollman, Councilors. **1939** Ernest W. Goodpasture, President; Shields Warren, Vice-President; Paul R. Cannon, Secretary-Treasurer; Jesse L. Bollman, Balduin Lucké, Councilors. **1940** Shields Warren, President; Jesse L. Bollman, Vice-President; H. P. Smith, Secretary-Treasurer; Balduin Lucké, Paul R. Cannon, Councilors. **1941** Jesse L. Bollman, President; Balduin Lucké, Vice-President; H. P. Smith, Secretary-Treasurer; Paul R. Cannon, Douglas H. Sprunt, Councilors. **1942,1943** Balduin Lucké, President; Paul R. Cannon, Vice-President; H. P. Smith, Secretary-Treasurer; Douglas H. Sprunt, Frieda S. Robscheit-Robbins, Councilors.

CONSTITUTION

Article I.—*Name*

The Society shall be named "The American Society for Experimental Pathology."

Article II.—*Object*

The object of this Society is to bring the productive investigators in pathology, working essentially by experimental methods, in closer affiliation with the workers in the other fields of experimental medicine.

Article III.—*Time and Place of Meeting*

The Society shall meet at the same time and place as the Federation of American Societies for Experimental Biology, which comprises at present the American Physiological Society, the American Society of Biological Chemists, the American Society for Pharmacology and Experimental Therapeutics, and the American Society for Experimental Pathology.

Article IV.—*Membership*

Section 1. Any American investigator who, through the use of experimental methods, has, within three years prior to his candidacy, contributed meritorious work in pathology, is eligible to membership.

Sec. 2. It shall be the policy of the Society to restrict its membership to as small numbers as is compatible with the maintenance of an active existence.

Sec. 3. There shall be two classes of members: active and honorary members.

Active members: Candidates for active membership shall be nominated at or before an annual meeting by two members of the Society. The nominators shall present to the Secretary in writing evidence of the candidate's qualifications for membership. Nominations approved by the Council shall be presented to the Society for election at the next annual meeting following nomination. For election a favorable ballot by a majority of the members present is necessary.

Honorary members: These may be elected from the active list or from the group of distinguished investigators at home or abroad who have contributed to the knowledge of pathology by experimental study. They shall be elected only by the unanimous vote of the members present at time of nomination.

Sec. 4. Active members shall pay such annual dues as are determined upon, from year to year, by the Council. Honorary members shall pay no dues, are not eligible to office, and have no vote in the business affairs of the Society, but they shall have all the privileges of the active members in the scientific proceedings.

Sec. 5. Upon failure of an active member to pay dues for two years, notice shall be given to the member by the Secretary. At the end of the third year, if dues are still unpaid, such failure constitutes forfeiture of membership.

Sec. 6. A motion for expulsion of a member must be thoroughly investigated by the Council; at this investigation the accused shall be afforded a hearing or may be represented by a member. Expulsion can be accomplished only after a unanimous vote by the Council in favor of expulsion, sustained by a four-fifths vote of the members present at the meeting.

Article V.—*Officers*

The management of the Society shall be vested in a Council of five members, consisting of a President, a Vice-President, a Secretary-Treasurer, and two other members who shall be nominated by the Council and elected by the Society. Officers are elected by a majority vote. Vacancies shall be filled by the Council for the unexpired term.

The President and Vice-President shall hold office for one year and are ineligible for re-election during the following year. The Secretary-Treasurer is eligible for re-election. Councilors shall hold office for two years and are elected on alternate years. At the first election one Councilor shall be elected for a short term of one year.

Article VI.—*Quorum*

Section 1. Three constitute a quorum of the Council. The Council decides by a majority vote.

Sec. 2. A quorum of the Society for transaction of business shall be one-fourth of the total mem-

bership. In all questions brought before the Society a majority vote of those present shall decide, except as elsewhere provided for.

ARTICLE VII.—*Annual Meeting*

SECTION 1. Papers shall be limited to ten minutes. However, on motion and with unanimous consent, the time may be prolonged by a period not exceeding five minutes. The Council may make provision for longer papers on suitable occasions.

SEC. 2. The subjects of papers must be confined to experimental work in pathology. In doubtful cases a liberal interpretation by the President and Secretary may prevail. The Council may invite, however, presentations dealing with any subject which it considers of considerable interest to the Society.

ARTICLE VIII.—*Change of Constitution*

A motion concerning a change of the Constitution must be presented to the Council in writing by three members, and must be communicated to the members by the Secretary at least four weeks before the annual meeting. At this meeting such a change may be established when accepted by a four-fifths vote of the members present.

BY-LAWS

1. There must be in each year at least one meeting of the Council, which shall take place not later than the evening before the annual meeting.

2. At the end of the first session of the annual meeting the Secretary shall read the report of the Council. This report shall include (1) names of persons recommended for membership, (2) nominations for offices, (3) matters of general interest. The Secretary shall exhibit in a conspicuous place the names of candidates for membership recommended by the Council, together with the evidence of the qualifications of the candidates.

3. The election of officers and of new members, changes in the Constitution, etc., shall be voted upon at the end of the first session.

4. Changes in the By-Laws may be determined by a majority vote of those present.

5. In the year that a new Secretary-Treasurer is elected the incoming Council Member elected that year, or another member of the Council, shall become Assistant Secretary-Treasurer for the duration of the term of the Secretary-Treasurer.

THE AMERICAN INSTITUTE OF NUTRITION

Founded April 11, 1933; Incorporated November 16, 1934
Member of Federation 1940

OFFICERS ELECTED 1944

President—ICIE G. MACY-HOOBLER
Vice-President—WM. C. ROSE
Secretary—ARTHUR H. SMITH
Treasurer—E. M. NELSON
Councilors—GENEVIEVE STEARNS, T. H. JUKES and C. A. ELVEHJEM.
Nominating Committee—H. A. MATTILL, Chairman, N. B. GUERRANT, J. C. WINTERS, A. A. HOGAN, F. J. STARE.

PAST OFFICERS

1933 L. B. MENDEL, President; H. C. SHERMAN, Vice-President; J. R. MURLIN, Secretary-Treasurer; E. F. DUBOIS, M. S. ROSE, Councilors. **1934** J. R. MURLIN, President; E. F. DUBOIS, Vice-President; ICIE G. MACY, Secretary; W. M. BOOTHBY, Treasurer; A. H. SMITH, AGNES FAY MORGAN, R. M. BETHKE, Councilors. **1935** J. R. MURLIN, President; E. F. DUBOIS, Vice-President; ICIE G. MACY, Secretary; G. R. COWGILL, Treasurer; A. H. SMITH, R. M. BETHKE L. A. MAYNARD, Councilors. **1936** E. F. DUBOIS, President; MARY SWARTZ ROSE, Vice-President; G. R. COWGILL, Treasurer; ICIE G. MACY, Secretary; R. M. BETHKE, L. A. MAYNARD, C. A. ELVEHJEM, Councilors. **1937** MARY S. ROSE, President; E. V. MCCOLLUM, Vice-President; G. R. COWGILL, Treasurer; ICIE G. MACY, Secretary; L. A. MAYNARD, C. A. ELVEHJEM, P. E. HOWE, Councilors. **1938** E. V. MCCOLLUM, President; T. M. CARPENTER, Vice-President; G. R. COWGILL, Treasurer; L. A. MAYNARD, Secretary; C. A. ELVEHJEM, P. E. HOWE, HELEN S. MITCHELL, Councilors. **1939** H. C. SHERMAN, President; T. M. CARPENTER, Vice-President; G. R. COWGILL, Treasurer; L. A. MAYNARD, Secretary; P. E. HOWE, HELEN S. MITCHELL, A. H. SMITH, Councilors. **1940** THORNE M. CARPENTER, President; A. G. HOGAN, Vice-President; L. A. MAYNARD, Secretary; W. H. SEBRELL, JR., Treasurer; HELEN S. MITCHELL, ARTHUR H. SMITH, LYDIA J. ROBERTS, Councilors. **1941** A. G. HOGAN, President; L. A. MAYNARD, Vice-President; ARTHUR H. SMITH, Secretary; W. H. SEBRELL, JR., Treasurer; T. H. JUKES, LYDIA J. ROBERTS, H. B. LEWIS, Councilors. **1942** L. A. MAYNARD, President; H. B. LEWIS, Vice-President; ARTHUR H. SMITH, Secretary; W. H. SEBRELL, JR., Treasurer; LYDIA J. ROBERTS, GENEVIEVE STEARNS, T. H. JUKES, Councilors. **1943** H. B. LEWIS, President; ICIE G. MACY-HOOB-

LER, Vice-President; ARTHUR H. SMITH, Secretary; LYDIA J. ROBERTS, GENEVIEVE STEARNS, T. H. JUKES, Councilors.

CONSTITUTION

1. The name of the proposed society is the "AMERICAN INSTITUTE OF NUTRITION."

2. The purposes of the society are to further the extension of the knowledge of nutrition and to facilitate personal contact between investigators in nutrition and closely related fields of interest.

3. The management of the American Institute of Nutrition shall be vested in a council consisting of the President, Vice-President, Secretary, Treasurer and three additional members.

BY-LAWS

ARTICLE I—*Membership*

SECTION 1. There shall be two classes of members, members and emeritus members. The number of members shall be limited to 300 exclusive of emeritus members.

SEC. 2. *Eligibility for membership:* Members. Qualified investigators who have independently conducted and published meritorious original investigations in some phase of the chemistry or physiology of nutrition and who have shown a professional interest in nutrition for at least 5 years shall be eligible for membership in the Society. Emeritus Members. Members in good standing who have reached the age of 65 years shall become emeritus members. A member in good standing and for sufficient reason may by vote of the Council be made an emeritus member. Emeritus members shall be entitled to vote but not hold office.

SEC. 3. *Nomination:* Nominations for membership shall be made and seconded by members of the Society on blanks furnished by the Secretary. Nominations shall be submitted to the Council who shall determine eligibility and make recommendation to the Society at a regular meeting.

SEC. 4. *Election to membership:* A. A nominee for membership may be voted for by ballot at any meeting of the Society after the Council has reported its findings on his eligibility. B. A majority of the ballots cast shall elect.

SEC. 5. *Forfeiture:* If a majority of the Council after due notice to the member in question and opportunity for a hearing, shall decide that the interests of the Society require the expulsion of a member, the Secretary shall send a notice of this decision to each member at least two weeks before the next annual meeting. At this meeting the Secretary shall, on behalf of the Council, propose the expulsion; and if two-thirds of the members present vote for it, the member shall be expelled, his assessment for the current year shall be returned to him, and he shall cease to be a member of the Society.

ARTICLE II—*Meetings and Quorum*

SECTION 1. *Annual:* The annual meeting of the Society shall be held on the date fixed by the Certificate of Incorporation.

SEC. 2. *Special:* A special meeting may be called at any time by the President, or in case of his absence or disability, by the Vice-President, and must be called at the request in writing of a majority of the Council or fifty members of the Society. Notice specifying the purpose of such meeting shall be mailed to each member at least ten days previous thereto. The Council shall select the places at which meetings shall be held.

SEC. 3. *Quorum:* Thirty members shall constitute a quorum at all meetings of the Society, but in the absence of a quorum any number shall be sufficient to adjourn to a fixed date.

ARTICLE III—*Officials*

SECTION 1. *Officers:* The officers shall be a President, and a Vice-President, who shall be elected annually, and a Secretary and Treasurer, each of whom shall be elected to serve for a term of three years. These officers shall be elected by the members of the Society. Their terms of office shall commence on May 1 of the year in which they are elected.

SEC. 2. *Council:* The officers so selected and three additional members, one of whom shall be elected at each annual meeting to serve a term of three years, shall constitute a Board of Trustees and shall be known as 'The Council.' (When this provision is first put into effect one member shall be elected for 1 year, one for 2 years and the third for 3 years.)

SEC. 3. *Duties of Officers:* The powers and duties of the officers elected by the Society shall be such as usually devolve upon their respective positions.

ARTICLE IV—*The Council*

SECTION 1. *Powers:* The general management of the Society during the intervals between meetings shall be vested in the Council, which shall regularly perform the ordinary duties of an executive committee and possess all the powers conferred upon the Board of Trustees of an educational institution chartered by the Education Department of the University of the State of New York. A permanent charter was issued to the American Institute of Nutrition under date of November 16, 1934.

SEC. 2. *Reports:* The Council shall report to the Society its findings on the eligibility of candidates for membership, and on all charges of a violation of these By-Laws.

ARTICLE V—*Nominating Committee*

SECTION 1. *Membership:* A. The Nominating Committee shall consist of five members appointed for the coming year by the retiring President. Members who have served on the Nominating Committee for two consecutive years shall be ineligible for reappointment until after a lapse of one year. B. The President shall designate one member to be Chairman of the Nominating Committee.

SEC. 2. *Nomination of Officials:* A. The Nominating Committee shall make at least one nomination for each of the four offices, for each of the additional positions on the Council to be filled by vote of the members and for each of the positions on the Editorial Board to be vacated at the time of the annual meeting. Any member of the Institute may submit nominations to the Nominating Committee for its consideration along with those nominations made by the members of the Nominating Committee. B. The nominations by the Nominating Committee shall be transmitted to the Secretary at least six weeks before the annual meeting at which they are to be considered. C. The Secretary shall send to every member, at least two weeks before the annual meeting, a printed ballot containing the list of nominees and space for such additional names as the member wishes to propose, and at the same time shall notify the members that they may vote by mail, returning to the Secretary the marked ballot in the envelope provided, at such a time and place as the Secretary may designate, or the ballot may be delivered to the Secretary at the beginning of the business session at which the elections are to take place.

SEC. 3. *Election of Officials:* A. At the beginning of the business session the Secretary shall present to the tellers, appointed by the President, the ballots submitted by the members and the ballots shall be counted forthwith. B. A majority of votes cast shall be necessary to elect an official.

SEC. 4. *Filling of Vacancies:* A. The Nominating Committee shall fill all vacancies in elective positions except such as may occur at a meeting of the Society. B. The President of the Society shall fill all vacancies in appointive positions.

ARTICLE VI—*Financial*

SECTION 1. *Dues:* The dues shall be the annual cost of subscription to The Journal of Nutrition for members plus an annual assessment which shall be determined by majority vote at the annual meetings, upon recommendation of the Council, and shall be due within a month after the annual meeting. Emeritus members are not required to subscribe to The Journal of Nutrition nor to pay assessments other than those levied on all members of the Federation by its Executive Committee.

SEC. 2. *Expenditures:* No expenditures from the general funds of the Society except those required in the performance of the ordinary official duties shall be made except by vote of the Society or the Council.

SEC. 3. *Penalty for non-payment of dues:* A. Members in arrears for dues for two consecutive years shall forfeit their membership. B. Delinquent members may be reinstated by the Council provided all indebtedness to the Society is liquidated.

ARTICLE VII—*The Journal of Nutrition*

SECTION 1. The American Institute of Nutrition designates The Journal of Nutrition as its official organ of publication.

SEC. 2. In accordance with the expressed wish of the Wistar Institute of Anatomy and Biology, owner and publisher of The Journal of Nutrition, the American Institute of Nutrition shall nominate members of the Editorial Board for its official organ. A. The editorial management of The Journal of Nutrition shall be vested in an Editorial Board consisting of an Editor and twelve Board Members. B. The Editor shall be chosen by the Editorial Board to serve a term of five years beginning May 1 of the year in which he is chosen, and shall be eligible for reëlection. The Editor shall have the power to designate one of the Board Members to serve as his assistant, and such an appointee shall be called Associate Editor. C. Three members of the Institute shall be nominated by the Nominating Committee for membership on the Editorial Board each year to serve a term of four years, replacing three retiring members and taking office May 1 of the year in which they are elected. In the event of a vacancy in the membership of the Editorial Board occurring through death or other reason, the Nominating Committee, for each such vacancy to be filled shall make an additional nomination. In this event the nominees elected who receive the greatest number of votes shall serve the longest term of vacancies to be filled. D. Retiring members of the Editorial Board shall not be eligible for renomination until one year after their retirement.

ARTICLE VIII—*Papers on Scientific Subjects*

SECTION 1. The Secretary shall be authorized to arrange programs for the scientific sessions at the annual meetings.

ARTICLE IX—*Changes in Constitution and By-Laws*

SECTION 1. Proposed changes in the Constitution and By-Laws must be sent in writing to the Secre-

tary at least one month before the date of the meeting at which they are to be considered, and must be signed by at least three members. The Secretary shall send a printed copy of any proposed change to each member at least two weeks before the next meeting and shall notify all members that they may vote by proxy.

SEC. 2. If at this meeting two-thirds of the votes cast shall favor the proposed change, it shall be made.

THE AMERICAN ASSOCIATION OF IMMUNOLOGISTS

Founded June 19, 1913; Member of Federation 1942

OFFICERS ELECTED 1942

President—JACQUES J. BRONFENBRENNER, Washington University School of Medicine, St. Louis, Mo.

Secretary-Treasurer—ARTHUR F. COCA, Pearl River, N. Y.

Council—JACQUES J. BRONFENBRENNER, ARTHUR F. COCA, MICHAEL HEIDELBERGER, 620 W. 168 St., New York City, PAUL R. CANNON, University of Chicago, Chicago, Ill., KARL F. MEYER, Medical Center, San Francisco, Cal., GEORGE P. BERRY, University of Rochester, Rochester, N. Y., DONALD T. FRASER, Connaught Laboratories, University of Toronto, Toronto, Canada, SANFORD B. HOOKER, (Ex officio), 80 East Concord St., Boston, Mass., JOHN F. ENDERS, (Ex officio), Harvard University School of Medicine, Boston, Mass.

PAST OFFICERS

Presidents—1913 GERALD B. WEBB. 1915 JAMES W. JOBLING. 1916 RICHARD WEIL. 1917 JOHN A. KOLMER. 1918 WILLIAM H. PARK. 1919 HANS ZINSSER. 1920 RUFUS I. COLE. 1921 FREDERICK P. GAY. 1922 GEORGE W. MCCOY. 1923 H. GIDEON WELLS. 1924 FREDERICK G. NOVY. 1925 WILFRED H. MANWARING. 1926 LUDVIG HEKTOEN. 1927 KARL LANDSTEINER. 1928 EUGENE L. OPIE. 1929 OSWALD T. AVERY. 1930 STANHOPE BAYNE-JONES. 1931 ALPHONSE R. DOCHEZ. 1932 AUGUSTUS B. WADSWORTH. 1933 THOMAS M. RIVERS. 1934 FRANCIS G. BLAKE. 1935 WARFIELD T. LONGCOPE. 1936 SANFORD B. HOOKER. 1937 CARL TENBROECK. 1938 DONALD T. FRASER. 1939 GEORGE P. BERRY. 1940 PAUL R. CANNON. 1941 KARL F. MEYER. 1942, 1943 JACQUES J. BRONFENBRENNER.

Vice-Presidents—1913–1915 GEORGE W. ROSS. 1915 GEORGE P. SANBORN. 1916 JOHN A. KOLMER.

Secretary—1913–1918 MARTIN J. SYNOTT.

Treasurer—1913—1918 WILLARD J. STONE.

Secretary-Treasurer—1918–*date*. ARTHUR F. COCA.

CONSTITUTION AND BY-LAWS

Adopted April 6, 1917

ARTICLE I

SECTION 1. This Association shall be called "The American Association of Immunologists."

SEC. 2. The purpose of the Association shall be to study the problems of immunology and its application to clinical medicine.

ARTICLE II

SECTION 1. The Association shall be governed by a Council of seven, which shall consist of the officers of the association and enough active members to make a total of seven members.

SEC. 2. The officers of the Association shall be a President, a Secretary, and a Treasurer, who shall be nominated annually by the Council, and elected by the Society to serve for one year. Nominations of officers may be made also by members of the Society.

SEC. 3. No councilor is eligible for re-election until after one year, except the Secretary and the Treasurer, who are eligible for re-election.

SEC. 4. If any councilor without good and sufficient reason fails to attend two consecutive meetings of the Council he shall be considered to have resigned.

SEC. 5. The same person shall not serve as President more than one year consecutively.

SEC. 6. It is the duty of the Council to conduct the business of the Association and to elect the new members. Should a vacancy occur in the Council otherwise than by the expiration of the term of service, the Council may elect a member to serve for the unexpired portion of the term.

ARTICLE III

SECTION 1. Active Members. Any one actively engaged in the systematic study of problems relating to immunology shall be eligible to active membership.

ARTICLE IV

Candidates for membership shall be nominated by two active members of the Association who shall present in writing to the Council evidence of the fitness of the candidates to become members of the Association.

ARTICLE V

If a majority of the Council shall decide that the interests of the Society require the expulsion of a

member, the Secretary shall send a notice of this decision to each active member at least two weeks before the next annual meeting. At this meeting the Secretary shall, on behalf of the Council, propose the expulsion; and if two-thirds of the members present vote for it, the member shall be expelled, his assessment for the current year shall be returned to him, and he shall cease to be a member of the Society.

Article VI

Section 1. A quorum of the Council for the transaction of all business shall be three.

Sec. 2. Any number of members present at the time appointed for the annual meeting of the Association, shall constitute a quorum.

BY-LAWS

1. A regular meeting of the Association shall be held annually at such time and place as the Council shall determine.

2. Special meetings of the Association may be held at the discretion of the Council.

3. These regular and special meetings shall be open to all members of the Association.

4. A meeting of the Council shall be held shortly before each annual session of the Association.

5. Hereafter each Councilor shall serve for a period of six years. Under this rule the service of one member and also that of the Secretary-Treasurer terminates at the meeting of 1936. At that meeting two members shall be elected to the Council, one of whom may serve as Secretary-Treasurer. Thereafter the period of service of these two members shall run concurrently; hence, two members must be elected to the Council every six years in order to maintain a membership of seven.

6. Past Presidents are honorary members of the Council.

7. The titles of all communications to be presented before the Association shall be approved by the Council.

8. Failure of an active member to offer a paper at least once in three years shall be equivalent to resignation. If in its judgment there is sufficient reason the Council may, in individual cases, suspend this rule.

9. The dues of the Association shall be fixed annually by the Council.

10. Failure to pay dues for three successive years shall constitute annulment of membership.

11. The constitution and by-laws may be amended by a two-thirds vote of the active members present at any regular meeting.

12. No amendment shall be adopted at the meeting at which it is proposed.

13. The Journal of Immunology, which is the property and official organ of this Association, shall be administered for the Association by an editorial staff to consist of an Editor-in-Chief and at least three Associate Editors, with the advice of a Board of Editors.

14. The members of the editorial staff shall be elected or may be removed by a majority vote of the Council of the Association.

ALPHABETICAL LIST OF ALL MEMBERS OF THE SIX SOCIETIES

The parenthesis following each listed name gives the Society affiliation and year of election:

(1) The American Physiological Society*
(2) The American Society of Biological Chemists
(3) The American Society for Pharmacology and Experimental Therapeutics
(4) The American Society for Experimental Pathology
(5) The American Institute of Nutrition
(6) The American Association of Immunologists

HONORARY MEMBERS

Castaneda, M. Ruiz, M.D. Investigaciones Medicas, Hospital General, Mexico, D. F. *Director, Department of Medical Research.* (6, 1942)

Chopra, R. N., M.A., M.D., Sc.D.(Cantab), F.R.C.P. (London) P.I.E. School of Tropical Medicine, Calcutta, India. *Director; Professor of Pharmacology.* (3, 1938)

Dale, H. H. Medical Research Council, National Institute for Medical Research, Hampstead, London, N.W. 3, England. *Director, National Institute for Medical Research.* (3, 1926)

Flexner, Simon, M.D., Sc.D.(hon.), LL.D. 520 E. 86th St., New York City. *Emeritus Director, Rockefeller Institute for Medical Research.* (6, 1920)

Hektoen, Ludvig, M.D. 629 S. Wood St., Chicago, Ill. *President, Chicago Tumor Institute.* (6, 1919)

Hitchens, Arthur P., M.D. Medical School, University of Pennsylvania, Philadelphia. *Professor of Public Health and Preventive Medicine; Lt. Col., M.C., U.S.A.* (6, 1913)

Houssay, Bernardo A., M.D. Viamonte 2790, Buenos Aires, Argentina. (1, 1942)

Huntoon, F. M., M.D. Woodbridge, Conn. (6, 1918)

Lowei, Otto, M.D. New York University College of Medicine, 477 First Ave., New York City *Research Professor in Pharmacology.* (3, 1941)

McCoy, George Walter, M.D. Louisiana State University Medical School, New Orleans. *Director, Department of Public Health.* (6, 1916)

Novy, Frederick G., M.D., Sc.D., LL.D. 721 Forest Ave., Ann Arbor, Mich. *Dean Emeritus and Professor Emeritus of Bacteriology, Medical School, University of Michigan.* (6, 1920)

Rosenau, Milton J., M.D., A.M. Medicai School, University of North Carolina, Chapel Hill. *Director, School of Public Health; Professor of Epidemiology, School of Public Health.* (6, 1918)

Sherrington, Sir Charles S., O.M., Sc.D., M.D., F.R.S. "Broomside," Valley Road, Ipswich, England. *Former Wayneflete Professor of Physiology, Oxford University; Former President of the Royal Society.* (1, 1904)

Sordelli, A. Institute of Bacteriology, Department of Public Health, Buenos Aires, Argentina. *Director.* (6, 1942)

Straub, Walther, M.D. University of Munich, Germany. (3, 1927)

MEMBERS

Abels, Jules C., M.D. Memorial Hospital, 444 E. 68th St., New York City. *Assistant Attending Physician.* (4, 1944)

Abramson, David Irwin, M.D. Percy Jones General Hospital, Springfield, Mo. *Captain, Medical Corps.* (1, 1937)

Abramson, Harold A., M.D. 133 E. 58th St., New York City. *Assistant Professor of Physiology, College of Physicians and Surgeons, Columbia University.* (1, 1930; 2, 1934)

Abreu, Benedict E., M.S., Ph.D., Division of Pharmacology, Univ. of California Medical School, San Francisco. *Assistant Professor of Pharmacology.* (3, 1941)

Acheson, George H., M.D. Harvard Medical School, 25 Shattuck St., Boston, Mass. *Associate in Pharmacology.* (1, 1942)

Adams, Mildred, M.A., Ph.D. Takamine Laboratory, Clifton, N. J. *Research Chemist.* (2, 1934)

Adams, R. Charles, M.D., C.M., M.S. (Anesthesiology), Mayo Clinic, Rochester, Minn. *Instructor in Anesthesia, Mayo Foundation, University of Minnesota. Member of Mayo Clinic Staff, Section on Anesthesia.* (3, 1942)

Adams, W. Lloyd, M.A., Ph.D. Albany Medical College, 357 Morris St., Albany, N. Y. *Assistant Professor of Physiology and Pharmacology.* (3, 1942)

Addis, Thomas, M.D., M.R.C.P. Lane Hospital, San Francisco, Calif. *Professor of Medicine, Stanford University.* (1, 1922)

Addison, William H. F., M.D. School of Medicine, University of Pennsylvania, Philadelphia. *Professor of Histology and Embryology.* (1, 1928)

* Recommended by the Council of the American Physiological Society for election at the next annual meeting of the Society.

Adler, Harry F., M.S., Ph.D.* Northwestern University Medical School, 303 E. Chicago Ave., Chicago, Ill. *Instructor in Physiology.* (1, 1943)

Adolph, Edward Frederick, Ph.D. School of Medicine and Dentistry, University of Rochester, Rochester, N. Y. *Associate Professor of Physiology.* (1, 1921)

Adolph, William H., Ph.D., 119 Eddy St., Ithaca, N. Y. (5, 1934)

Albanese, Anthony A., Ph.D. The Johns Hopkins Hospital, Baltimore, Md. *Associate in Pediatrics, Department of Pediatrics, The Johns Hopkins University.* (2, 1944)

Albritton, Errett C., M.D. George Washington University Medical School, 1339 H St., N.W., Washington, D. C. *Professor of Physiology and Head of the Department of Physiology.* (1, 1933)

Allen, Charles Robert, Ph.D.* University of Texas, School of Medicine, Galveston. *Assistant Professor of Department of Anesthesiology.* (1, 1943)

Allen, Frank N., M.D. Lahey Clinic, 605 Commonwealth Ave., Boston, Mass. *Co-director of the Medical Department.* (4, 1930)

Allen, Frederick M., M.D. 1031 Fifth Ave., New York City. *Professor of Medicine, Polyclinic Medical School and Hospital.* (1, 1924; 4, prior to 1920)

Allen, J. Garrott, M.D.* University of Chicago, University Clinics, Chicago, Ill. *Instructor in Surgery.* (1, 1943)

Allen, Lane, M.S., Ph.D., M.D. University of Georgia School of Medicine, University Place, Augusta. *Associate Professor of Anatomy.* (1, 1939)

Allen, Willard M., M.D. Washington University School of Medicine, 630 S. Kingshighway Blvd., St. Louis, Mo. *Professor of Obstetrics and Gynecology.* (1, 1934)

Allen, William F., Ph.D. University of Oregon Medical School, Portland. *Professor of Anatomy.* (1, 1929)

Alles, Gordon A., M.S., Ph.D. 770 S. Arroyo Parkway, Pasadena, Calif. *Lecturer in Pharmacology, University of California Medical School, San Francisco, and Research Associate in Biology, California Institute of Technology, Pasadena.* (1, 1932; 3, 1941)

Almquist, Herman J., Ph.D. F. E. Boothby Laboratories, 1290 Powell St., Emeryville, Calif. *Director of Poultry Husbandry, University of California.* (2, 1937; 5, 1937)

Alvarez, Walter C., M.D. Mayo Clinic, Rochester, Minn. *Professor of Medicine, Mayo Foundation.* (1, 1917; 3, 1921)

Alving, Alf Sven, M.D. Billings Hospital, University of Chicago, 950 E. 59th St., Chicago, Ill. *Associate Professor of Medicine.* (1, 1939)

Amberg, Samuel, M.D., F.A.A.P. Mayo Clinic, Rochester, Minn. *Associate in Pediatrics, Mayo Clinic; Associate Professor of Pediatrics, Mayo Foundation* (1, 1903; 2, 1906; 3, 1909)

Amberson, William R., Ph.D. University of Maryland School of Medicine, Baltimore. *Professor of Physiology.* (1, 1924)

Ambrose, Anthony M., M.S., Ph.D. Western Regional Research Laboratory, 800 Buchanan St., Albany, Calif. *Associate Pharmacologist, U. S. Department of Agriculture, Bureau of Agricultural Chemistry and Engineering.* (3, 1937)

Amoss, Harold L., M.D., M.S., Dr.P.H., Sc.D. 21 Field Point Road, Greenwich, Conn. (4, 1922; 6, 1917)

Andersch, Marie A., Ph.D. University Hospital, Baltimore, Md. *Biochemist, University Hospital, Instructor in Medicine, University of Maryland.* (2, 1940)

Andersen, Dorothy H., M.D. Babies Hospital, Broadway and 167th St., New York City. *Associate in Pathology, Columbia University.* (4, 1935)

Anderson, Evelyn M., M.A., M.D. University of California Hospital, San Francisco. *Assistant Professor of Medicine.* (1, 1934)

Anderson, Hamilton H., M.S., M.D. Pharmacology Laboratory, Univ. of California Medical School, San Francisco. *Professor of Pharmacology.* (3, 1931)

Anderson, Oscar Daniel, Ph.D. Stimson Hall, Cornell University, Ithaca, N. Y. *Assistant Professor of Physiology.* (1, 1939)

Anderson, Rudolph J., Ph.D. Sterling Laboratory, Yale University, New Haven, Conn. *Professor of Chemistry.* (2, 1915)

Anderson, W. A. D., M.A., M.D. St. Louis University School of Medicine, St. Louis, Mo. *Associate Professor of Pathology.* (4, 1941)

Anderson, William E., M.A. Eastern State Farmers' Exchange, Westbrook Farm, Rockville, Conn. *Biochemist.* (2, 1931; 5, 1933)

Andervont, H. B., Sc.D. National Cancer Institute, Bethesda, Md. *Principal Biologist, U. S. Public Health Service.* (4, 1939)

Andrews, James C., Ph.D. University of North Carolina, Chapel Hill. *Professor of Biological Chemistry and Nutrition.* (2, 1925)

Andrus, E. Cowles, M.D. Johns Hopkins Hospital, Baltimore, Md. *Assistant Visiting Physician; Associate Professor of Medicine, Johns Hopkins University.* (1, 1925)

Angerer, Clifford, Ph.D.* Ohio State University, Columbus. *Instructor in Physiology.* (1, 1943)

Angevine, D. Murray, M.D. Alfred I. du Pont Institute, Wilmington, Del. *Pathologist; Visiting Assistant Professor of Pathology, University of Pennsylvania.* (4, 1940)

Angier, Roswell Parker, Ph.D. c/o Los Ranchos Perkins, Tucson, Ariz. *Professor of Psychology, Yale University.* (1, 1906)

Ansbacher, Stefan, M.S., D.Sc. American Home Products Corp., Products Development Laby., 350 Fifth Ave., New York City. *Scientific Director.* (2, 1939)

Anson, Mortimer L., Ph.D. 25 Central Park West, New York City. Continental Foods, Inc., Hoboken, N. J. *Director of Biochemical Research.* (2, 1937)

Apperly, Frank L., M.A., D.Sc., M.D., F.R.C.P. Medical College of Virginia, Richmond. *Professor of Pathology.* (4, 1936)

Arkin, Aaron, M.A., M.D., Ph.D. Suite 2006, 25 E. Washington St., Chicago, Ill. *Professor of Medicine, Rush Medical College, Univ. of Chicago; Professor and Chairman, Dept. of Medicine, Cook County Graduate School.* (1, 1914; 3, 1919)

Armstrong, W. D., M.S., M.D., Ph.D. Medical Sciences Bldg., University of Minnesota, Minneapolis. *Professor of Physiological Chemistry.* (2, 1938)

Arnold, Lloyd, A.M., M.D. 1538 E. 57th St., Chicago, Ill. (4, 1930; 6, 1925)

Arnow, L. Earle, Ph.D., M.D. Medical Research Division, Sharp and Dohme, Glenolden, Pa. *Director of Research.* (2, 1940)

Aronson, Joseph D., M.D. *Associate Professor of Bacteriology, Phipps Institute, University of Pennsylvania; Lt. Col., M.C., 361st Med. Composite Detachment (Lab.) Camp Ellis, Ill.* (4, 1927; 6, 1925)

Artom, Camillo, M.D. Bowman Gray School of Medicine, Winston-Salem, N. C. *Professor of Biochemistry.* (2, 1944)

Ascham, Leah, Ph.D. Kansas State College, Manhattan. *Associate Professor, School of Home Economics.* (5, 1935)

Asenjo, Conrado F., Ch.E., M.S., Ph.D. Dept. of Chemistry, School of Tropical Medicine, Box 4509, San Juan, Puerto Rico. *Assistant Professor of Chemistry and Acting Head of Department, School of Tropical Medicine of the University of Puerto Rico under the Auspices of Columbia University.* (2, 1944)

Ashby, Winifred M., Ph.D. 305 10th St., N.E., Washington, D. C. *Senior Scientist, Federal Security Agency (St. Elizabeth's Hospital).* (6, 1923)

Ashman, Richard, M.S., Ph.D. School of Medicine, Louisiana State University, New Orleans. *Professor of Physiology.* (1, 1925)

Astwood, Edwin Bennet, M.D., C.M., Ph.D. Harvard Medical School, 25 Shattuck St., Boston, Mass. *Assistant Professor of Pharmacotherapy.* (1, 1939)

Aub, Joseph C., M.D. Collis P. Huntington Memorial Hospital, 695 Huntington Ave., Boston, Mass. *Associate Professor of Medicine, Harvard Medical School.* (1, 1919; 5, 1933)

Auer, John, M.D. 1402 S. Grand Blvd., St. Louis, Mo. *Professor of Pharmacology and Director of the Department, St. Louis University School of Medicine.* (1, 1905; 3, 1908)

Austin, J. Harold, M.D. 711 Maloney Clinic, 36th and Spruce Sts., Philadelphia, Pa. *Director, Pepper Laboratory.* (2, 1922)

Austin, Richard Sisson, M.D. Cincinnati General Hospital, University of Cincinnati, Cincinnati, O. *Professor of Pathology.* (4, 1927)

Avery, O. T., M.D., Sc.D., LL.D. Hospital of the Rockefeller Institute, 66th St. and York Ave., New York City. *Member Emeritus, Rockefeller Institute for Medical Research.* (4, 1921; 6, 1920)

Axtmayer, Joseph H., A.M., Ph.D. School of Tropical Medicine, San Juan, Porto Rico. *Associate Professor of Chemistry.* (5, 1935)

Babkin, B. P., M.D., D.Sc., F.R.S.C. McGill University, Montreal, Canada. *Professor of Physiology.* (1, 1924)

Bachem, Albert, Ph.D. College of Medicine, University of Illinois, 1853 W. Polk St., Chicago. *Professor of Biophysics.* (1, 1933)

Bachman, Carl, M.D. Mobile Hospital No. 5, c/o Fleet P. O., San Francisco, Calif. *Lieut. Commander.* (2, 1941)

Bachmann, George, M.S., M.D., F.A.C.P. 1088 Lullwater Road, N.E., Atlanta, Ga. *Professor of Physiology, Emory University School of Medicine.* (1, 1912)

Baer, Erich, Ph.D. Banting Institute, 100 College St., Toronto, Canada. *Assistant Research Professor of Organic Chemistry, University of Toronto.* (2, 1942)

Baernstein, Harry D., M.S., Ph.D. National Institute of Health, Bethesda, Md. *Biochemist.* (2, 1934)

Baetjer, Anna M., D.Sc. Johns Hopkins School of Hygiene and Public Health, 615 N. Wolfe St., Baltimore, Md. *Associate in Physiology.* (1, 1929)

Bahrs, Alice M., M.A., Ph.D. The Martha Washington Hotel, 10th and Montgomery Sts., Portland, Ore. (1, 1933)

Bailey, Cameron Vernon, M.D., C.M. 303 E. 20th St., New York City. *Clinical Professor of Medicine, New York Post-Graduate Medical School, Columbia University.* (2, 1920; 5, 1933)

Bailey, Orville T., M.D. Harvard University Medical School, 25 Shattuck St., Boston, Mass. *Associate in Pathology.* (4, 1939)

Bailey, Percival, M.D., Ph.D. University of Illinois College of Medicine, 912 S. Wood St., Chicago. *Professor of Neurology and Neurosurgery.* (1, 1941)

Baitsell, George Alfred, A.M., Ph.D. Yale Station, New Haven, Conn. *Professor of Biology, Yale University.* (1, 1915)

Baker, A. B., M.D. University of Minnesota Medical School, 126 Millard Hall, Minneapolis. *Associate Professor of Neuropsychiatry and Neuropathology.* (4, 1940)

Baker, Roger D., M.D. Duke Hospital, Durham, N. C. *Associate Professor of Pathology in Charge of Surgical Pathology, Duke University Medical School; Associate Pathologist, Duke Hospital.* (4, 1939)

Baldes, Edward J., A.M., Ph.D. Mayo Foundation, Rochester, Minn. *Assistant Professor of Physics, Mayo Foundation, Graduate School, University of Minnesota.* (1, 1930)

Baldwin, Francis Marsh, A.M., Ph.D. University of Southern California, Los Angeles. *Professor of Zoology and Director of Experimental Marine Biology.* (1, 1919)

Bale, William F., Ph.D.* University of Rochester, School of Medicine and Dentistry, Rochester, N. Y. *Associate in Radiology.* (1, 1943)

Ball, Eric G., M.A., Ph.D. Harvard Medical School, Boston, Mass. *Associate Professor of Biological Chemistry.* (2, 1934)

Ball, Howard A., M.D. San Diego County General Hospital, N. Front St., San Diego, Calif. *Pathologist, San Diego County General and Paradise Valley Hospitals.* (4, 1937)

Balls, Arnold Kent, Ph.D. Enzyme Research Laboratory, U. S. Bureau of Agricultural and Industrial Chemistry, Western Regional Research Laboratory, 800 Buchanan St., Albany 6, Calif. *Head Chemist; Adjunct Professor, The George Washington University* (on leave). (2, 1932)

Banus, Mario Garcia, M.Sc., D.Sc. Tufts College Medical School, Boston, Mass. *Associate Professor of Physiology.* (1, 1927)

Bard, Philip, A.M., Ph.D. Johns Hopkins University School of Medicine, 710 N. Washington St., Baltimore, Md. *Professor of Physiology; Member National Academy of Sciences.* (1, 1929)

Barkan, Georg, M.D., Dr. habil. 80 E. Concord St., Boston, Mass. *Former Professor of Pharmacology and Director of the Pharmacological Institute, Univ. of Dorpat (Estonia); Assistant Professor of Biochemistry, Boston University School of Medicine.* (3, 1939)

Barker, S. B., Ph.D. College of Medicine, State University of Iowa, Iowa City. *Assistant Professor of Physiology.* (1, 1938)

Barlow, O. W., Ph.D., M.D. Nutrition Research Laboratories, 4210 Peterson Ave., Chicago, Ill. *Medical and Research Director.* (1, 1936; 3, 1944)

Barnes, B. O., A.M., Ph.D. 2220 S. St. Paul, Denver, Colo. *Professor of Health Education, University of Denver.* Station Hospital, KAAF, Kingman, Ariz. (1, 1932)

Barnes, LaVerne A., M.S., PhD. 5515 Maple Ave., Bethesda, Md. *Lieutenant, H-V(S), U.S.N.R. (Epidemiology and Sanitation Unit, National Naval Medical School).* (6, 1931)

Barnes, Richard Henry, Ph.D. Dept. of Physiology, University of Minnesota, Minneapolis. *Assistant Professor, Physiological Chemistry.* (2, 1941; 5, 1944)

Barnes, Thomas C., D.Sc. Hahnemann Medical College, Philadelphia, Penna. *Associate Professor of Physiology.* (1, 1942)

Barott, Herbert G., E.E. U. S. Department of Agriculture, National Agricultural Research Center, Beltsville, Md. *Biophysicist, Animal Nutrition Division, Bureau of Animal Industry.* (5, 1938)

Barrera, S. Eugene, M.D. Albany Medical College, New Scotland Ave., Albany, N. Y. (1, 1937)

Barron, Donald H., M.S., Ph.D., M.A. (Cambridge)* Yale University School of Medicine, New Haven, Conn. *Associate Professor of Physiology.* (1, 1943)

Barron, E. S. Guzman, M.D. Department of Medicine, University of Chicago, Chicago, Ill. *Associate Professor of Biochemistry.* (2, 1931)

Bartley, S. Howard, Ph.D. Dartmouth Eye Institute, Dartmouth College, Hanover, N. H. *Assistant Professor of Research in Physiological Optics.* (1, 1935)

Bass, Allan D., M.S., M.D. c/o G. C. Thompson, Manchester, Ga. *Professor of Pharmacology, Syracuse University. On leave of absence in the Service.* (3, 1944)

Batchelder, Esther L., A.M., Ph.D. Rhode Island State College, School of Agriculture and Home Economics, Kingston. *Head of Department of Home Economics.* (5, 1933)

Bates, Robert W., Ph.D. Difco Laboratories, Inc., 920 Henry St., Detroit, Mich. *Biochemist.* (2, 1936)

Batterman, Robert C., M.D. New York University College of Medicine, 477 First Ave., New York City. *Instructor in Therapeutics.* (3, 1941)

Baudisch, Oskar, Ph.D. Saratoga Springs, N. Y. *Director of Research, Saratoga Springs Authority, State of New York.* (2, 1931)

Bauer, Johannes H., M.D. Rockefeller Foundation, 49 W. 49th St., New York City. *Member of Staff, International Health Division of the Rockefeller Foundation.* (4, 1935)

Bauer, Walter, M.D. Massachusetts General Hospital, Boston. *Associate Professor and Tutor in Medicine, Harvard Medical School; Colonel, MC, Army Service Forces Hq. 8th Service Command, Dallas, Texas.* (1, 1929)

Bauman, Louis, M.D. Presbyterian Hospital, New York City. *Assistant Professor of Clinical Medicine, Columbia University.* (2, 1912)

Baumann, Carl A., M.S., Ph.D. Biochemistry Dept., University of Wisconsin, Madison.

Associate Professor of Biochemistry. (2, 1938; 5, 1938)

Baumann, Emil J., Ph.D. 7 Church Lane, Scarsdale, N. Y. *Chemist, Montefiore Hospital.* (2, 1922)

Baumberger, J. Percy, M.S., Sc.D. Stanford University, Calif. *Professor of Physiology.* (1, 1921)

Bayne-Jones, Stanhope, M.D. Yale University, School of Medicine, New Haven, Conn. *Professor of Bacteriology.* (4, 1927; 6, 1917)

Bazett, Henry C., M.A., M.D., F.R.C.S. University of Pennsylvania, School of Medicine, Philadelphia. *Professor of Physiology.* (1, 1921)

Beach, Eliot F., Ph.D. 2nd Port Headquarters, Surgeon's Office, APO 322, San Francisco, Calif. Captain, Sanitary Corps. (2, 1941; 5, 1942)

Bean, John W., M.S., Ph.D., M.D. University of Michigan, Ann Arbor. *Associate Professor of Physiology.* (1, 1932)

Beard, Howard H., M.A., Ph.D. 1542 Tulane Ave., New Orleans, La. *Professor of Biochemistry, Louisiana State University Medical Center.* (2, 1928; 5, 1933)

Beard, Joseph W., M.D. Duke Hospital, Durham, N. C. *Associate Professor of Surgery.* (4, 1938; 6, 1940)

Beazell, James Myler, Ph.D., M.D. 2118 Hayden, Amarillo, Texas. *Captain, MC, AUS; Instructor in Physiology and Pharmacology, Northwestern University School of Medicine.* (1, 1939)

Beck, Claude S., M.D. Lakeside Hospital, Cleveland, O. *Professor of Neurosurgery, Western Reserve University; Associate Surgeon, Lakeside Hospital.* (4, 1930)

Beck, Lyle V., M.S., Ph.D. Hahnemann Medical College, 235 N. 15th St., Philadelphia, Pa. *Associate Professor of Physiology.* (1, 1941)

Becker, Ernestine, M.A. Johns Hopkins University, Baltimore, Md. *Associate in Biochemistry.* (5, 1938)

Becker, R. Frederick, M.S., Ph.D. Northwestern University Medical School, 303 E. Chicago Ave., Chicago, Ill. *Instructor in Anatomy.* (1, 1941)

Becker, Theodore J., M.A., Ph.D. Winthrop Chemical Co., Rensselaer, N. Y. *Research Pharmacologist.* (3, 1944)

Beckman, Harry, M.D. Marquette University School of Medicine, Milwaukee, Wis. *Professor and Director of the Department of Pharmacology.* (3, 1937)

Beecher, Henry K., M.D. Massachusetts General Hospital, Boston. *Dorr Professor of Research in Anaesthesia, Harvard Medical School; Anesthetist-in-Chief, Massachusetts General Hospital.* (3, 1940)

Behre, Jeanette Allen, Ph.D. Department of Biochemistry, College of Physicians and Surgeons, 630 W. 168th St., New York City. *Associate.* (2, 1925)

Belding, David L., M.D. Boston University School of Medicine, Boston, Mass. *Professor of Bacteriology and Experimental Pathology.* (4, 1927)

Bell, E. T., M.D. 110 Anatomy Bldg., University of Minnesota, Minneapolis. *Professor of Pathology.* (4, 1931)

Benedict, Francis Gano, Ph.D., Sc.D., M.D. Machiasport, Me. *Former Director of the Nutrition Laboratory of the Carnegie Institution of Washington; Member of the National Academy of Sciences.* (1, 1904; 2, 1906)

Bennett, A. Lawrence, Ph.D., M.D. College of Medicine, University of Nebraska, Omaha. *Professor of Physiology and Pharmacology.* (1, 1941)

Bennett, Granville A., M.D. University of Illinois College of Medicine, 1853 West Polk Street, Chicago. *Professor of Pathology.* (4, 1931)

Bennett, Mary Adelia, M.A., Ph.D. Lankenau Hospital Research Institute, Philadelphia, Pa. *Research Biochemist.* (2, 1941)

Benson, Clara C., Ph.D. 157 Bloor St., W., Toronto, Canada. *Professor of Food Chemistry, University of Toronto.* (2, 1906)

Berg, Benjamin N., M.D. 630 W. 168th St., New York City. *Associate in Pathology, Columbia University, College of Physicians and Surgeons.* (4, 1928)

Berg, Clarence P., M.A., Ph.D. Chemistry Department, State University of Iowa, Iowa City. *Associate Professor of Biochemistry.* (2, 1933; 5, 1936)

Berg, William N., Ph.D. 225 W. 106th St., New York City. *Biochemist.* (2, 1906)

Bergeim, Olaf, M.S., Ph.D. 1853 W. Polk St., Chicago, Ill. *Associate Professor of Physiological Chemistry, University of Illinois College of Medicine.* (1, 1916; 2, 1914, 5, 1933)

Bergmann, Werner, Ph.D. Sterling Chemistry Building, Yale University, New Haven, Conn. *Associate Professor.* (2, 1934)

Berkson, Joseph, M.A., M.D., D.Sc. 2141 Eye St., N.W., Washington, D. C. *Associate Professor, Biometry and Medical Statistics, Mayo Foundation, University of Minnesota. Col. AUS.* (1, 1933)

Bernheim, Frederick, Ph.D. Box 3109, Duke Medical School, Durham, N. C. *Associate Professor of Physiology and Pharmacology.* (2, 1933; 3, 1935)

Bernthal, Theodore G., M.S., M.D. Vanderbilt University School of Medicine, Nashville, Tenn. *Associate Professor of Physiology.* (1, 1932)

Berry, George Packer, M.D. University of Rochester, Rochester, N. Y. *Assistant Dean;*

Professor of Bacteriology; Associate Professor of Medicine. (4, 1938; 6, 1934)

Bessey, Otto A., Ph.D. Public Health Research Institute of the City of New York, Inc., foot of E. 15th St., New York. *Chief, and Director, Division of Nutrition and Physiology.* (2, 1938; 5, 1943)

Best, Charles Herbert, M.A., M.D., D.Sc. (London), D.Sc. (Chicago), F.R.S. University of Toronto, Toronto, Ont., Canada. *Director, Banting and Best Department of Medical Research and Department of Physiology.* (1, 1923; 2, 1923)

Bethell, Frank H., M.D. 409 Lenawee Drive, Ann Arbor, Mich. *Assistant Professor of Internal Medicine and Assistant Director of the Thomas Henry Simpson Memorial Institute.* (4, 1936)

Bethke, Roland M., M.S., Ph.D. Ohio Agricultural Experiment Station, Wooster. *In Charge of Nutritional Investigations.* (2, 1928; 5, 1933)

Beutner, R., M.D., Ph.D. 235 N. 15th St., Philadelphia, Pa. *Professor and Head of Department of Pharmacology, Hahnemann Medical College.* (1, 1924; 3, 1924)

Beyer, Karl H., Ph.D., M.D. Medical-Research Division, Sharp and Dohme, Inc., Glenolden, Pa. *Director of Pharmacological Research.* (1, 1942; 3, 1944)

Bieter, Raymond N., M.D., Ph.D. University of Minnesota, Minneapolis. *Professor of Pharmacology.* (3, 1930)

Bills, Charles E., M.A., Ph.D. Mead Johnson & Co., Evansville, Ind. *Director of Research.* (2, 1928; 5, 1935)

Bing, Franklin C., Ph.D. 1135 Fullerton Ave., Chicago, Ill. *Director, American Institute of Baking; Assistant Professor of Physiology, Northwestern University Medical School.* (2, 1931; 5, 1934)

Bing, Richard J., M.D. The Johns Hopkins Hospital, Dept. of Medicine, Baltimore, Md. *Instructor in Medicine, Associate Physician to the Johns Hopkins Hospital.* (1, 1942)

Binger, Carl A., M.D. 125 E. 73rd St., New York City. *Assistant Professor of Clinical Medicine (Psychiatry), Cornell University Medical College.* (1, 1927)

Binkley, Stephen Bennett, M.S., Ph.D. Research Department, Parke, Davis & Co., Detroit, Mich. (2, 1941)

Bisbey, Bertha, A.M., Ph.D. Gwynn Hall, University of Missouri, Columbia. *Professor of Home Economics.* (5, 1933)

Bischoff, Fritz E., M.S., Ph.D. Cottage Hospital, Santa Barbara, Calif. *Director of Research.* (2, 1928; 5, 1933)

Bishop, George H., Ph.D. Washington University Medical School, Euclid and Kingshighway, St. Louis, Mo. *Professor of Bio-Physics.* (1, 1923)

Biskind, Gerson R., M.D. Mt. Zion Hospital, San Francisco, Calif. *Pathologist, Mt. Zion Hospital; Clinical Instructor in Pathology, University of California Medical School.* (4, 1944)

Black, Edgar C., Ph.D.* Dept. of Physiology, Dalhousie Univ., Halifax, Nova Scotia, Canada. (1, 1943)

Blair, Edgar A., M.S., Ph.D. U. S. Army, General Section T.I.S., Fort Benning, Ga. *Lt. Col.* (1, 1936)

Blair, Henry A., M.Sc., Ph.D. University of Rochester School of Medicine and Dentistry, Rochester, N. Y. *Associate Professor of Physiology.* (1, 1934)

Blake, Francis G., M.D., M.A. (hon.), Sc.D. Yale University School of Medicine, New Haven, Conn. *Dean and Sterling Professor of Medicine.* (4, prior to 1920; 6, 1921)

Blankenhorn, M. A., M.D. University of Cincinnati, Cincinnati, O. *Professor of Medicine.* (4, 1932)

Blatherwick, Norman R., M.S., Ph.D., Sc.D. Metropolitan Life Ins. Co., 1 Madison Ave., New York City. *Director of Biochemical Laboratory.* (1, 1915; 2, 1915; 5, 1934)

Blau, Nathan F., Ph.D. American Ferment Company, 942 Prospect St., Trenton, N. J. *Chief Chemist.* (2, 1928)

Blish, Morris J., M.A., Ph.D. Amino Products Company, Rossford, O. *Research Director, Division of International Minerals and Chemical Corp.* (2, 1944)

Bliss, Chester Ittner, Ph.D. Conn. Agr. Expt. Sta., P. O. Box 1106, New Haven. *Biometrician, Lecturer in Biometry, Yale University.* (3, 1944)

Bliss, Eleanor A., Sc.D. Department of Preventive Medicine, Johns Hopkins Hospital, 615 N. Wolfe St., Baltimore, Md. *Associate in Preventive Medicine, Johns Hopkins University, School of Medicine.* (6, 1931)

Bliss, Sidney, Ph.D. Tulane University, New Orleans, La. *Professor of Biochemistry, School of Medicine.* (2, 1928)

Bloch, Konrad, Ph.D. 630 W. 168th St., New York, N. Y. *Instructor in Biochemistry, Columbia University.* (2, 1944)

Block, Richard J., Ph.D. 15 Cooper Rd., Scarsdale, N. Y. *Director of Research, C. M. Armstrong Co.; Associate, Department of Physiology and Biochemistry, New York Medical College, Flower and Fifth Avenue Hospital.* (2, 1934; 5, 1933)

Block, Walter D., M.S., Ph.D. University Hospital, Ann Arbor, Mich. *Instructor in Biological Chemistry, Rackham Arthritis Research Unit.* (2, 1942)

Bloom, William, M.D. 1419 E. 56th St., Chicago, Ill. *Professor of Anatomy, University of Chicago.* (4, 1930)

Bloomfield, A. L., M.D. Stanford University Hospital, San Francisco, Calif. *Professor of Medicine.* (3, 1927; 4, 1927)

Bloor, W. R., A.M., Ph.D. School of Medicine and Dentistry, University of Rochester, Rochester, N. Y. *Professor of Biochemistry.* (1, 1915; 2, 1910)

Blum, Harold F., Ph.D. Naval Medical Research Institute, National Naval Medical Center, Bethesda, Md. *Principal Biologist (Biophysics).* (1, 1928)

Blumberg, Harold, D.Sc. The Johns Hopkins University, Baltimore, Md. *Research Biochemist.* (5, 1942)

Blumenstock, Julius, M.D. 530 Larkin St., San Francisco, Calif. *Captain, Medical Corps.* (1, 1925)

Blumgart, Herrmann L., M.D. Beth Israel Hospital, 330 Brookline Ave., Boston, Mass. *Associate Professor of Medicine, Harvard Medical School; Lt. Col., M.C., Hdqtrs., 2nd Service Command, Governor's Island, N. Y.* (1, 1927)

Blunt, Katharine, Ph.D., LL.D. 38 Glenwood Ave., New London, Conn. *President Emeritus, Connecticut College for Women.* (2, 1921)

Bock, Joseph C., Ch.E., Ph.D. 2324 N. 46th St., Milwaukee, Wis. *Professor Emeritus of Biochemistry, Marquette University Medical School.* (2, 1916)

Bodansky, Aaron, Ph.D. Hospital for Joint Diseases, 1919 Madison Ave., New York City. *Biological Chemist.* (2, 1926)

Bodansky, Oscar, M.D., Ph.D. Medical Research Laboratory, Edgewood Arsenal, Md. *Major, Medical Corps; Chief, Biochemistry Section, Medical Research Laboratory, Medical Division, Chemical Warfare Service.* (2, 1937; 3, 1942)

Bodine, Joseph Hall, Ph.D. State University of Iowa, Iowa City. *Professor and Head of Department of Zoology.* (1, 1925)

Boell, Edgar J., Ph.D. Osborn Zoological Laboratory, Yale University, New Haven, Conn. *Associate Professor of Biology.* (1, 1942)

Bogert, L. Jean, Ph.D. Hotel Claremont, Berkeley, Calif. (2, 1917)

Bogert, Marston Taylor, Sc.D., LL.D., R.N.D. Columbia University, New York 27, N. Y. *Professor Emeritus of Organic Chemistry; Member. National Academy of Sciences.* (2, 1925)

Bolliger, Adolph, Ph.D. Gordon Craig Research Laboratories, University of Sydney, Sydney, Australia. *Director of Research.* (2, 1928)

Bollman, J. L., M.D. Mayo Clinic, Rochester, Minn. *Associate in Division of Experimental Surgery and Pathology, Mayo Clinic; Professor of Physiology, Mayo Foundation, University of Minnesota.* (4, 1927)

Bond, Glenn C., Ph.D., M.D. The Upjohn Co., Research Laboratories, Kalamazoo, Mich. (6, 1939)

Booher, Lela E., Ph.D. General Mills, Inc., Minneapolis, Minn. *Chief, Nutritionist.* (2, 1933; 5, 1933)

Bookman, Samuel, M.A., Ph.D. 624 Madison Ave., New York City. *Consulting Chemist, Mt. Sinai Hospital.* (2, 1912)

Boor, Alden K., M.S., Ph.D. Department of Medicine, University of Chicago, Chicago, Ill. *Assistant Professor of Biochemistry.* (2, 1931)

Boothby, W. M., M.D., M.A., F.A.C.S. Metabolism Laboratory, The Mayo Clinic, Rochester, Minn. *Chief of Section of Clinical Metabolism in Division of Medicine, Mayo Clinic; Professor of Experimental Metabolism, Mayo Foundation, University of Minnesota; Chairman, Mayo Aero-Medical Unit; Member Subcommittee on Oxygen and Anoxia, N.R.C., O.S.R.D.* (1, 1915; 2, 1920; 3, 1923; 4, 1924)

Bordley, James, III, M.D. Johns Hopkins Hospital, Baltimore, Md. *Associate Professor of Medicine, Johns Hopkins University.* (1, 1938)

Borsook, Henry, M.D., Ph.D. California Institute of Technology, Pasadena 4. *Professor of Biochemistry.* (2, 1931)

Bosworth, Alfred Willson, A.M., M.D. R. D. 4, Circleville, O. *Consulting Chemist.* (2, 1936; 5, 1935)

Bott, Phyllis A., M.S., Ph.D. Woman's Medical College of Pennsylvania, East Falls, Philadelphia. *Associate Professor of Physiological Chemistry.* (2, 1938)

Bouman, H. D., M.D.* Northwestern Univ. Med. School, 303 E. Chicago Ave., Chicago, Ill. *Assistant Professor of Physical Medicine and Physiology.* (1, 1943)

Bourne, Wesley, M.D., C.M., M.Sc., F.R.C.P., D.A. (R.C.P. & S., Eng.). McGill University, Montreal, Canada. *Lecturer in Anesthetics, Dept. of Pharmacology and Therapeutics.* (3, 1936)

Bourquin, Helen, M.S., Ph.D. 1331 N. Tejon St., Colorado Springs, Colo. (1, 1925)

Bowman, Donald E., A.M., Ph.D. 6956 Warwick Rd., Indianapolis, Ind. *Assistant Professor of Biochemistry, Indiana University School of Medicine.* (2, 1944)

Boyd, Eldon M., M.A., M.D., C.M. Queen's University, Kingston, Ontario, Canada. *Professor and Head of the Department of Pharmacology.* (3, 1941)

Boyd, T. E., Ph.D. 706 S. Lincoln St., Chicago, Ill. *Professor of Physiology, Loyola University School of Medicine.* (1, 1924)

Boyd, William C., A.M., Ph.D. Boston University School of Medicine, 80 E. Concord St., Boston, Mass. *Associate Professor of Biochemistry.* (2, 1940; 6, 1933)

Boyden, Edward A., A.M., Ph.D. University of Minnesota, Minneapolis. *Professor of Anatomy and Chairman of the Department.* (1, 1929)

Boyer, Paul D., M.S., Ph.D. Department of Chemistry, Stanford University, Calif. *Research Associate.* (2, 1944)

Boyle, Paul E., D.M.D. School of Dentistry, University of Pennsylvania, 40th and Spruce Sts., Philadelphia. (4, 1939)

Bozler, Emil, Ph.D. Ohio State University, Columbus. *Associate Professor of Physiology.* (1, 1932)

Bradbury, James T., M.S., ScD. Dept. of Obstetrics and Gynecology, University Hospitals, Iowa City. *Assistant Professor of Obstetrics and Gynecology* (1, 1941)

Bradley, Harold C., Ph.D. Shorewood Hills, Madison, Wis. *Professor of Physiological Chemistry, University of Wisconsin.* (1, 1911; 2, 1908)

Bradley, William B., Ph.D. 3646 Lafayette Ave., Omaha, Neb. *Captain, A. C., Chatham Field, Ga.* (1, 1939)

Branch, Charles F., M.D. Boston University School of Medicine, 80 E. Concord St., Boston, Mass. *Professor of Pathology.* (4, 1940)

Branch, E. Arnold G., M.D. Bureau of Laboratories, General Hospital, St. John, N. B. *Acting Director, Bureau of Laboratories, New Brunswick Department of Health.* (4, 1929)

Brand, Erwin, Ph.D. 630 W. 168th St., New York City. *Associate Professor of Biological Chemistry, Columbia University.* (2, 1929)

Brandes, W. W., M.D. Roosevelt Hospital, W. 59th St., New York City. (4, 1931)

Branham, Sara E., Ph.D., M.D., Sc.D. National Institute of Health, Bethesda, Md. *Senior Bacteriologist.* (6, 1926)

Branion, Hugh Douglas, M.A., Ph.D. 50 James St., Guelph, Canada. (5, 1933)

Brassfield, Charles R., Ph.D. University of Michigan, Ann Arbor. *Assistant Professor of Physiology.* (1, 1937)

Bratton, Andrew Calvin, Jr., M.A., Ph.D. Johns Hopkins School of Medicine, Baltimore, Md. *Associate in Pharmacology.* (3, 1941)

Braun, Herbert A., Ph.D. Food & Drug Administration, Federal Security Agency, Washington, D. C. *Associate Pharmacologist.* (3, 1941)

Brewer, George, M.D. University of Pennsylvania, School of Medicine, Philadelphia. *Assistant Professor of Physiology.* (1, 1937)

Bridge, Edward M., M.D. 219 Bryant St., Buffalo, N. Y. *Research Professor of Pediatrics.* (2, 1940)

Briggs, A. P., M.D. University of Georgia, Augusta. *Associate Professor in Biochemistry and Medicine.* (2, 1923)

Brink, Frank, Jr., Ph.D. Johnson Research Foundation, University of Pennsylvania, Philadelphia. *Fellow in Medical Physics, Johnson Research Foundation; Lecturer in Biophysics, Graduate School, University of Pennsylvania.* (1, 1942)

Brinkhous, K. M., M.D. State University of Iowa, Department of Pathology, Medical Laboratories Building, Iowa City. *Assistant Professor of Pathology.* (4, 1939)

Britton, Sydney W., M.D. University of Virginia School of Medicine, University. *Professor of Physiology.* (1, 1925)

Brobeck, John R., M.D., Ph.D.* Yale University School of Medicine, New Haven, Conn. *Instructor, Laboratory of Physiology.* (1, 1943)

Brodie, Bernard B., Ph.D. N. Y. University Research Service, Goldwater Memorial Hospital, New York City. *Research Associate in Biochemistry and Assistant Professor of Pharmacology, New York University Medical College.* (2, 1940)

Brody, Samuel, M.A., Ph.D. Dairy Building, University of Missouri, Columbia. *Associate Professor, College of Agriculture and Agricultural Experiment Station.* (2, 1929; 5, 1933)

Bronfenbrenner, J. J., Ph.D., D.P.H. Washington University School of Medicine, St. Louis, Mo. *Professor of Bacteriology and Immunology.* (4, 1940; 6, 1918)

Bronk, Detlev W., M.S., Ph.D., Sc.D. The Eldridge Reeves Johnson Foundation for Medical Physics, University of Pennsylvania, Philadelphia. *Johnson Professor of Biophysics and Director, Johnson Foundation; Member National Academy of Sciences.* (1, 1927)

Brookes, Margaret C. Hessler, A.M., Ph.D. University of Chicago, Chicago, Ill. *Assistant Professor, Department of Home Economics.* (5, 1935)

Brooks, Chandler McCuskey, M.A., Ph.D. Johns Hopkins University School of Medicine, Baltimore, Md. *Associate Professor of Physiology.* (1, 1934)

Brooks, Clyde, Ph.D., M.D., LL.D. Louisiana State Univ. Medical Center, New Orleans. *Professor of Physiology and Pharmacology.* (1, 1910; 3, 1912)

Brooks, Matilda Moldenhauer, M.S., Ph.D. Department of Zoology, University of California, Berkeley. *Research Associate in Biology.* (1, 1923)

Brooks, Sumner Cushing, Ph.D. University of California, Berkeley. *Professor of Zoology.* (1, 1923)

Broun, Goronwy Owen, M.D. 1325 S. Grand Blvd., St. Louis, Mo. *Professor of Internal Medicine, St. Louis University.* (4, 1927)

Brown, Aaron, M.D. 39 West 55th St., New York City. *Assistant Clinical Professor of Medicine, New York University College of Medicine.* (6, 1923)

Brown, Claude P., M.D. 1930 Chestnut St., Philadelphia, Pa. *Assistant Director, Pennsylvania State Board of Health Laboratories.* (6, 1913)

Brown, Dugald E. S., M.A., Ph.D. New York University College of Dentistry, 209 E. 23rd St., New York City. *Professor of Physiology.* (1, 1932)

Brown, Edgar D., Pharm.D., M.D. Paynesville, Minn. *Associate Professor of Pharmacology Emeritus.* (1, 1907; 3, 1909)

Brown, Frank A., Jr., M.A., Ph.D. Zoological Laboratories, Northwestern University, Evanston, Ill. *Associate Professor of Zoology.* (1, 1940)

Brown, John B., M.S., Ph.D. Ohio State University, Columbus. *Professor of Physiological Chemistry.* (2, 1927; 5, 1934)

Brown, Rachel, M.S., Ph.D. 26 Buckingham Drive, Albany, N. Y. *Senior Biochemist, Division of Laboratories and Research, New York State Department of Health.* (6, 1933)

Browne, J. S. L., M.D., Ph.D., F.R.S.C. University Clinic, Royal Victoria Hospital, Montreal, Canada. *Assistant Professor of Medicine, McGill University.* (1, 1934)

Brownell, Katharine A., M.A., Ph.D.* Department of Physiology, Ohio State University, Columbus. *Research Associate.* (1, 1943)

Brues, Austin M., M.D. Metallurgical Laboratory, University of Chicago, Chicago 80, Ill. *Assistant Professor of Medicine, Harvard Medical School; Assistant Physician, Mass. General Hospital.* (1, 1940)

Bruger, Maurice, M.D., C.M., M.Sc. 245 E. 17th St., New York 3, N. Y. *Associate Clinical Professor of Medicine, New York Post-Graduate Medical School of Columbia University; Chief, Division of Pathological Chemistry, New York Post-Graduate Hospital.* (2, 1935; 5, 1935)

Bruhn, John M., Ph.D. University of Alabama School of Medicine, University. *Professor of Physiology and Pharmacology.* (1, 1939).

Brunschwig, Alexander, M.D. University of Chicago, Chicago, Ill. *Professor of Surgery.* (4, 1937)

Bryan, W. Ray, Ph.D. 5516 Johnson Ave., Bethesda, Md. *Biologist, National Cancer Institute.* (1, 1934; 4, 1940)

Buchanan, J. William, Ph.D. Northwestern University, Evanston, Ill. *Professor of Zoology.* (1, 1927)

Buchbinder, Leon, Ph.D. Department of Health, 125 Worth St., New York City. (6, 1934)

Buchbinder, William C., M.S., M.D. 104 S. Michigan Ave., Chicago, Ill. *Assistant Professor of Medicine, Northwestern University Medical School; Associate in Medicine, Michael Reese Hospital.* (1, 1940)

Buckner, G. Davis, Ph.D. Kentucky Agricultural Experiment Station, Lexington. *In Charge of Animal Nutrition.* (2, 1920)

Bucy, Paul C., M.S., M.D. 25 E. Washington St., Chicago, Ill. *Professor of Neurology and Neurological Surgery, University of Illinois.* (1, 1933)

Buddingh, G. John, M.D. Vanderbilt University School of Medicine, Nashville, Tenn. *Associate Professor of Bacteriology.* (4, 1940)

Buell, Mary Van Rensselaer, Ph.D. Johns Hopkins Hospital, Baltimore, Md. *Associate in Medicine.* (2, 1921)

Bugbee, Edwin P., M.D. Lankenau Hospital, Philadelphia, Pa. *Assistant Roentgenologist.* (1, 1928)

Bugher, John C., M.D. c/o Rockefeller Foundation, 49 W. 49th St., New York City. (4, 1934)

Bukantz, Samuel C., M.D. 8712 Colesville Rd., Silver Spring, Md. *Chief, Division of Virus and Rickettsial Diseases, Army Medical School, Washington, D. C.* (6, 1943)

Bulatao, Emilio, M.D. University of the Philippines, Manila, P.I. *Professor of Physiology.* (1, 1924)

Bulger, Harold A., Ph.D., M.D. Barnes Hospital, 600 S. Kingshighway, St. Louis, Mo. *Assistant Professor of Medicine, Washington University.* (5, 1933)

Bull, Henry B., Ph.D. Northwestern University Medical School, 303 E. Chicago Ave., Chicago, Ill. *Associate Professor, Department of Chemistry.* (2, 1937)

Bunde, Carl A., M.A., Ph.D.* Southwestern Medical Foundation, Dallas, Texas. *Associate Professor of Physiology and Pharmacology.* (1, 1943)

Bunney, William E., Ph.D. E. R. Squibb & Sons, New Brunswick, N. J. *Director of Biologic Products Production.* (6, 1931)

Bunting, Charles H., M.D. Service Memorial Institute, Madison, Wis. *Professor of Pathology, University of Wisconsin.* (4, 1913)

Bunzell, H. H., Ph.D. Box 44, General Post Office, New York 1, N. Y. *Director, Bunzell Laboratories.* (2, 1908)

Burchell, Howard B., M.D., Ph.D. 799 3rd St., S.W., Rochester, Minn. *Instructor in Medicine, Mayo Foundation, Graduate School, University of Minnesota; Consultant in Medicine, Mayo Clinic, Rochester, Minn.* (1, 1942)

Burdick, H. O., M.A., Sc.D. (hon.). Alfred University, Alfred, N. Y. *Professor of Biology* (1, 1940)

Burdon, Kenneth L., Sc.M., Ph.D. Baylor University College of Medicine, Houston, Texas

Professor of Bacteriology; Consultant, United States Public Health Service. (6, 1936)

Burge, W. E., A.M., Ph.D. University of Illinois, Urbana. *Associate Professor of Physiology.* (1, 1911)

Burk, Dean, Ph.D. National Cancer Institute, U. S. Public Health Service, Bethesda, Md. *Senior Chemist.* (2, 1939)

Burky, Earl L., M.S., M.D. Johns Hopkins Hospital, Baltimore, Md. *Associate Professor of Ophthalmology, Wilmer Institute of Ophthalmology, Johns Hopkins University.* (6, 1931)

Burnett, Theo. C., M.D. Box 216, Carmel, Calif. *Associate Professor of Physiology Emeritus, University of California.* (1, 1911)

Burns, Edward L., M.D. Louisiana State University, School of Medicine, New Orleans. *Associate Professor of Pathology and Bacteriology.* (4, 1939)

Burr, George O., M.A., Ph.D., LL.D. University of Minnesota, Minneapolis. *Director Division of Physiological Chemistry.* (2, 1928; 5, 1933)

Burrill, Marie Wecker, Ph.D. *542½ Surf St., Chicago, Ill. *Instructor in Physiology, Northwestern University Medical School.* (1, 1944)

Burrows, Montrose T., M.D. 201 N. El Molino Ave., Pasadena, Calif. (4, prior to 1920)

Burton, Alan C., Ph.D. Banting Institute, Toronto, Canada. (1, 1937)

Burton-Opitz, Russell, M.S., M.D., Ph.D. 218 Bridle Way, Palisade, N. J. *Attending Cardiologist, Lenox Hill Hospital; Attending Physician, Cumberland Hospital; Consulting Cardiologist, Engelwood, North Hudson, Holy Name and Hackensack Hospitals.* (1, 1902; 2, 1906; 3, 1919)

Bush, Milton T., Ph.D. Vanderbilt University School of Medicine, Nashville, Tenn. *Research Associate in Pharmacology.* (3, 1938)

Butler, Thomas C., M.D. Vanderbilt University School of Medicine, Nashville, Tenn. *Assistant Professor of Pharmacology.* (3, 1938)

Butt, Hugh R., M.D. U. S. Naval Hospital, Corona, Calif. (5, 1942)

Butts, Joseph S., M.S., Ph.D. Personal Equipment Laboratory, Wright Field, Dayton, O. *Major, A.U.S., Chief, Survival Unit.* (2, 1936; 5, 1936)

Butz, Eleanor W. J., Ph.D. Beltsville, Md. *Collaborator, Div. Animal Husbandry, U. S. D. A., Beltsville Research Center.* (6, 1935)

Cahill, William M., Ph.D. Wayne University College of Medicine, Detroit, Mich. *Assistant Professor of Physiological Chemistry.* (2, 1940)

Cajori, Florian A., Ph.D. School of Military Government, Charlottesville, Va. *Major, Sanitary Corps, A.U.S.* (2, 1922; 5, 1933)

Caldwell, Mary L., A.M., Ph.D. Department of Chemistry, Columbia University, New York City. *Associate Professor of Chemistry.* (2, 1924; 5, 1933)

Calvery, Herbert O., M.S., Ph.D. Food and Drug Administration, Federal Security Agency, Washington 25, D. C. *Chief, Division of Pharmacology.* (2, 1928; 3, 1939)

Calvin, D. Bailey, M.A., Ph.D. School of Medicine, University of Texas, Galveston. *Associate Professor, Biological Chemistry; Associate Dean, School of Medicine.* (1, 1934; 2, 1939)

Cameron, A. T., M.A., D.Sc., F.I.C., F.R.S.C. Medical College, Winnipeg, Manitoba, Canada. *Professor of Biochemistry, Faculty of Medicine, University of Manitoba; Biochemist, Winnipeg General Hospital.* (1, 1914; 2, 1914)

Camp, Walter J. R., M.D., Ph.D. 1853 Polk St., Chicago, Ill. *Professor of Pharmacology and Therapeutics, University of Illinois.* (3, 1926)

Campbell, Dan H., M.S., Ph.D. Department of Chemistry, California Institute of Technology, Pasadena, Calif. *Assistant Professor of Immunochemistry.* (6, 1938)

Campbell, H. Louise, Ph.D. 435 W. 119th St., Apt. 9-F, New York City. *Research Assistant in Food Chemistry, Columbia University.* (5, 1933)

Campbell, James, M.A , Ph.D.* University of Toronto, Toronto, Ontario, Canada. *Assistant Professor of Physiology. Lieutenant Commander, (S.B.) R.C.N.V.R.* (1, 1943)

Campbell, Walter Ruggles, M.A., M.D., F.R.C.P. (C), F.R.S.C. 69 Madison Ave., Toronto, Canada. *Assistant Professor of Medicine and Clinical Medicine, University of Toronto; Assistant Physician, Toronto General Hospital.* (2, 1922)

Cannan, R. Keith, D.Sc. 477 First Ave., New York City. *Professor of Chemistry, New York University College of Medicine.* (2, 1931)

Cannon, Paul R., M.D., Ph.D. University of Chicago, Chicago, Ill. *Professor of Pathology.* (4, 1930; 6, 1929)

Cannon, Walter B., A.M., M.D., Sc.D., LL.D. Harvard Medical School, Boston, Mass. *George Higginson Professor of Physiology, Harvard University; Member of the National Academy of Sciences.* (1, 1900)

Cantarow, Abraham, M.D. Jefferson Medical College, Philadelphia, Pa. *Associate Professor of Medicine; Biochemist to the Jefferson Hospital.* (1, 1932; 3, 1935)

Canzanelli, Attilio, M.D. Tufts College Medical School, 416 Huntington Ave., Boston, Mass. *Associate Professor in the Department of Physiology.* (1, 1934)

Carlson, A. J., A.M., Ph.D., M.D., LL.D. Hull Physiological Laboratory, University of Chicago, Chicago, Ill. *Professor of Physiology Emeritus; Member of the National Academy of Sciences.* (1, 1904; 5, 1933)

Carmichael, Emmett B., Ph.D. School of Medicine, University of Alabama, University. *Professor of Physiological Chemistry.* (1, 1931)

Carmichael, Leonard, Ph.D., Sc.D., Litt.D., LL.D. Tufts College, Medford, Mass. *Director, the Tufts College Research Laboratory of Sensory Psychology and Physiology and President of the College.* (1, 1937)

Carpenter, Thorne M., Ph.D. 29 Blackfan St., Boston, 15, Mass. *Director, Nutrition Laboratory of the Carnegie Institution of Washington.* (1, 1915; 2, 1909; 5, 1935)

Carr, C. Jelleff, Ph.D. School of Medicine, University of Maryland, Baltimore. *Associate Professor of Pharmacology.* (3, 1940)

Carr, Jesse L., M.D. University of California Medical School, Third and Parnassus Aves., San Francisco. *Assistant Professor of Pathology.* (4, 1940)

Carter, Herbert E., M.A., Ph.D. 452 Noyes Laboratory, Urbana, Ill. *Associate Professor of Biochemistry, University of Illinois.* (2, 1937; 5, 1941)

Cartland, George F., M.S., Ph.D. The Upjohn Co., Research Department, Kalamazoo, Mich. *Biochemist and Pharmacologist.* (2, 1936)

Cary, Charles A., S.B. Dairy Research Laboratory, Beltsville, Md. *Chief, Division of Nutrition and Physiology, Bureau of Dairy Industry, U. S. Department of Agriculture.* (2, 1920)

Casey, Albert Eugene, M.D. Jefferson and Baptist Hospitals, Birmingham, Ala. *Pathologist.* (4, 1933)

Cash, James Robert, M.D. University Hospital, Charlottesville, Va. *Professor of Pathology, University of Virginia.* (4, 1924)

Castle, Edward S., M.A., Ph.D. Biological Laboratories, Harvard University, Divinity Ave., Cambridge, Mass. *Assistant Professor of General Physiology.* (1, 1934)

Castle, William B., M.D., S.M. (Hon. Yale), M.D. (Hon. Utrecht). Boston City Hospital, Boston, Mass. *Professor of Medicine, Harvard Medical School; Associate Director, Thorndike Memorial Laboratory and Director, II and IV Medical Services (Harvard), Boston City Hospital.* (4, 1942)

Catchpole, Hubert Ralph, Ph.D. National Naval Medical Center, Bethesda, Md. *Ensign, USNR; Research Assistant in Physiology (Assistant Professor), Yale University Medical School.* (1, 1941)

Cathcart, E. P., M.D., D.Sc., LL.D. University of Glasgow, Glasgow, Scotland. *Dean of University.* (5, 1935)

Catron, Lloyd, M.D. The City Hospital, Akron, O. *Pathologist.* (4, 1939)

Cattell, McKeen, A.M., Ph.D., M.D. Cornell University Medical College, 1300 York Ave., New York City. *Professor of Pharmacology.* 1, 1923; 3, 1924)

Cerecedo, Leopold R., Ph.D. Fordham University, New York City. *Professor of Biochemistry.* (2, 1931)

Chadwick, Leigh Edward, Ph.D.* University of Rochester School of Medicine and Dentistry, 260 Crittenden Blvd., Rochester, N. Y. *Instructor in Physiology.* (1, 1944)

Chaikoff, I. L., A.M., Ph.D., M.D. University of California, Berkeley. *Assistant Professor of Physiology.* (1, 1932)

Chalkley, Harold W., A.M., Ph.D. U. S. Public Health Service, National Institute of Health, Bethesda, Md. *Senior Physiologist.* (1, 1932)

Chambers, Leslie Addison, M.S., Ph.D. Johnson Foundation for Medical Physics, University of Pennsylvania, Philadelphia. *Lecturer in Biophysics; Associate in Medical Physics; Associate in Pediatrics.* (1, 1940)

Chambers, Robert, A.M., Ph.D. New York University, Washington Square East, New York City. *Research Professor of Biology.* (1, 1932)

Chambers, William H., M.S., Ph.D. Cornell University Medical College, 1300 York Ave., New York City. *Associate Professor of Physiology. Major, Sn.C. AUS* (1, 1924; 5, 1933)

Chandler, Caroline A., M.D. National Institute of Health, Bethesda, Md. (6, 1938)

Chandler, Joseph P., M.S., Ph.D. Cornell University Medical College, 1300 York Ave., New York City. *Assistant Professor of Biochemistry.* (2, 1944; 5, 1944)

Chanutin, Alfred, Ph.D. Box 1038 (University Station), Charlottesville, Va. *Professor of Biochemistry, University of Virginia.* (2, 1925)

Chapman, C. W., M.Sc., Ph.D. University of Maryland, Baltimore. *Professor of Pharmacology.* (3, 1932)

Chargaff, Erwin, Ph.D. Columbia University, College of Physicians and Surgeons, 630 W. 168th St., New York City. *Assistant Professor of Biological Chemistry.* (2, 1935)

Charipper, Harry Adolph, M.S., Ph.D. Washington Square College of Arts and Sciences, 100 Washington Square East, New York City. *Professor of Biology and Chairman of the Department.* (1, 1941)

Chase, Aurin M., A.M., Ph.D. Department of Biology, Princeton University, Princeton, N. J. *Research Associate.* (1, 1939)

Chase, Harold F., M.D. Western Reserve University School of Medicine, Cleveland, O. *Assistant Professor of Pharmacology.* (3, 1944)

Chase, Merrill W., M.S., Ph.D. Rockefeller Institute, 66th St. and York Ave., New York City. *Member of Staff.* (6, 1938)

Chasis, Herbert, M.D., Med. Sc.D. 44 E. 67th St., New York City. *Assistant Professor of*

Medicine, New York University, College of Medicine. (1, 1941)

Chatfield, Charlotte, B.S. U. S. Dept. of Agriculture, Washington, D. C. *In Charge, Food Composition Section, Bureau of Home Economics.* (5, 1941)

Chen, Graham, Sc.D., M.D. Dept. of Pharmacology, University of Chicago, Chicago, Ill. *Research Associate (Assistant Prof.).* (3, 1944)

Chen, K. K., Ph.D., M.D. The Lilly Research Laboratories, Indianapolis, Ind. *Director of Pharmacological Research; Professor of Pharmacology, Indiana University School of Medicine, Indianapolis.* (1, 1929; 3, 1942)

Cheney, Ralph H., A.M., M.S., Sc.D. Long Island University, 600 Lafayette Ave., Brooklyn, N. Y. *Chairman, Biology Department.* (3, 1934)

Chesney, Alan M., M.D. The Johns Hopkins Hospital, Baltimore, Md. *Dean, Johns Hopkins Medical School; Associate Professor of Medicine.* (4, 1925)

Child, Charles Manning, Ph.D., D.Sc. (hon.). Jordon Hall, Stanford University, Calif. *Member, National Academy of Sciences; Professor Emeritus, University of Chicago.* (1, 1923)

Chow, Bacon, Ph.D. Squibb Institute for Medical Research, New Brunswick, N. J. *Associate in the Division of Pharmacology.* (2, 1940)

Christensen, L. Royal, Ph.D. New York University College of Medicine, 477 First Ave., New York City. *Medical Fellow, National Research Council.* (6, 1942)

Christian, Henry A., M.D. 20 Chapel St., Brookline, Mass. *Hersey Professor of the Theory and Practice of Physic, Emeritus, Harvard University, recalled to active teaching; Clinical Professor of Medicine, Tufts College Medical School; Physician-in-Chief, Emeritus, Peter Bent Brigham Hospital, Boston; Visiting Physician, Beth Israel Hospital, Boston.* (4, 1924)

Christman, Adam A., Ph.D. University of Michigan Medical School, Ann Arbor. *Associate Professor of Physiological Chemistry.* (2, 1929)

Clark, Ada R., M.A., Ph.D. College of Physicians and Surgeons, 630 W. 168th St., New York City. *Instructor in Bacteriology.* (6, 1936)

Clark, Byron B., M.S., Ph.D. Albany Medical College, Albany, N. Y. *Associate Professor of Physiology and Pharmacology.* (3, 1940)

Clark, Eliot R., M.D. University of Pennsylvania, Philadelphia. *Professor and Head of Department of Anatomy.* (1, 1919)

Clark, Ernest D., A.M., Ph.D. 826 Skinner Bldg., Seattle 1, Wash. *Director of the Laboratories, Northwest Branch, National Canners' Association.* (2, 1912)

Clark, George, Ph.D.* Yerkes Laboratory of Primate Biology, Orange Park, Fla. *Assistant Professor of Psychobiology.* (1, 1943)

Clark, Guy W., A.M., Ph.D. c/o Lederle Laboratories, Inc., Pearl River, N. Y. *Technical Director.* (2, 1922)

Clark, Janet Howell, A.M., Ph.D. Anderson Hall, University of Rochester, Rochester, N. Y. *Dean of the College for Women and Professor in the Division of Biological Sciences.* (1, 1922)

Clark, Paul F., Ph.D. University of Wisconsin Medical School, Madison. *Professor of Bacteriology.* (4, 1923; 6, 1928)

Clark, William G., Ph.D. Department of Physiology, University of Southern California, Los Angeles 7. (1, 1942)

Clark, William Mansfield, M.A., Ph.D., D.Sc. Johns Hopkins University, Baltimore, Md. *Professor of Physiological Chemistry; Member National Academy of Sciences.* (2, 1920)

Clarke, Hans Thacher, D.Sc. (London), F.I.C. 630 W. 168th St., New York City. *Professor of Biological Chemistry, Columbia University, College of Physicians and Surgeons.* (2, 1929)

Clarke, Robert W., Ph.D. Yale University School of Medicine, 333 Cedar St., New Haven, Conn. *Instructor in Physiology.* (1, 1936)

Clausen, Samuel Wolcott, M.D. Strong Memorial Hospital, Rochester, N. Y. *Professor of Pediatrics, School of Medicine, University of Rochester.* (2, 1922)

Cleghorn, Robert Allen, M.D., D.Sc. (Aberdeen). Department of Medicine, University of Toronto, Toronto, Ont., Canada. *Junior Demonstrator in Medicine; Junior Assistant Attending Physician, Toronto General Hospital.* (1, 1937)

Climenko, David Robert, M.D., Ph.D. Winthrop Chemical Co., 33 Riverside Ave., Rensselaer, N. Y. *Pharmacologist; Associate in Biochemistry and Instructor in Medicine, Albany Medical College.* (1, 1933)

Clowes, George Henry Alexander, Ph.D., D.Sc. (hon.), LL.D. (hon.). Eli Lilly & Co., Indianapolis, Ind. *Director of Research.* (2, 1914; 6, 1919)

Coca, Arthur F., A.M., M.D. Pearl River, N. Y. *Medical Director, Lederle Laboratories.* (6, 1916)

Code, Charles F., Ph.D., M.D. Mayo Foundation, Rochester, Minn. *Professor of Physiology.* (1, 1939)

Coffey, Julia M., A.B. Division of Laboratories & Research, New York State Department of Health, Albany, N. Y. *Associate Bacteriologist.* (6, 1937)

Coghill, Robert D., M.S., Ph.D. Northern Regional Research Laboratory, U. S. Department of Agriculture, Peoria, Ill. *Chief, Fermentation Division.* (2, 1932)

Cohen, Barnett, M.S., Ph.D. Johns Hopkins University School of Medicine, 710 N. Wash-

ington St., Baltimore 5, Md. *Associate Professor of Physiological Chemistry.* (2, 1935)

Cohen, Milton B., M.D. 10616 Euclid Ave., Cleveland, O. *Director, The Asthma, Hay Fever and Allergy Foundation.* (6, 1931)

Cohen, Philip P., Ph.D., M.D. Service Memorial Institute, University of Wisconsin, Madison. *Assistant Professor of Clinical Chemistry.* (2, 1941)

Cohen, Sophia M., B.S. Division of Laboratories and Research, New York State Department of Health, Albany, N. Y. *Assistant Bacteriologist.* (6, 1938)

Cohn, Alfred E., M.D. 300 Central Park W., New York City. *Member, Rockefeller Institute for Medical Research.* (1, 1911; 3, 1913)

Cohn, Edwin J., Ph.D., A.M. (Hon.), Sc.D. (Hon.). 183 Brattle St., Cambridge, Mass. *Professor of Biological Chemistry, Harvard Medical School, Boston; Member, National Academy of Sciences.* (1, 1919; 2, 1919)

Cohn, Waldo E., M.S., Ph.D. 109 Marion Rd., Oak Ridge, Tenn. *Chief Biochemist, Clinton Laboratories, Knoxville, Tenn.* (2, 1944)

Cole, Arthur G., Ph.D. 1853 W. Polk St., Chicago 12, Ill. *Assistant Professor of Physiological Chemistry, University of Illinois College of Medicine.* (2, 1939)

Cole, Harold N., M.D. 1352 Hanna Bldg., Cleveland, O. *Clinical Professor of Dermatology and Syphilology, Western Reserve University.* (3, 1925)

Cole, Kenneth S., Ph.D. 5618 Kimbark Ave., Chicago, Ill. (1, 1934)

Cole, Rufus, M.D., D.Sc. Mount Kisco, N. Y. *Member Emeritus, Rockefeller Institute for Medical Research.* (4, 1924; 6, 1917)

Cole, Versa V., Ph.D., M.D. Indiana University School of Medicine, 1040–1232 West Michigan St., Indianapolis. *Assistant Professor of Pharmacology.* (3, 1941)

Collett, Mary Elizabeth, A.M., Ph.D. Mather College, Western Reserve University, Cleveland, O. *Associate Professor of Biology.* (1, 1921)

Collier, H. Bruce, M.A., Ph.D. Dalhousie University, Halifax, N. S. *Associate Professor of Biochemistry.* (2, 1944)

Collings, William Doyne, Ph.D.* University of Texas School of Medicine, Galveston. *Assistant Professor of Physiology.* (1, 1944)

Collins, Dean A., M.A., Ph.D., M.D. University of Illinois, College of Medicine, 1853 West Polk St., Chicago. *Associate Professor of Physiology.* (1, 1938)

Collins, Russell J., A.M., M.D., F.R.C.P. (Can.) M.R.C.P. (Edin.) F.A.C.P. St. John, New Brunswick, Canada. *Medical Superintendent of St. John Tuberculosis Hospital.* (3, 1915)

Collip, J. B., A.M., Ph.D., D.Sc., M.D., C.B.E. McGill University, Montreal, Quebec, Canada. *Director, Research Institute of Endocrinology.* (1, 1920; 2, 1920)

Colowick, Sidney P., Ph.D. Dept. of Pharmacology, Washington University Medical School, Euclid and Scott Aves., St. Louis, Mo. *Instructor in Pharmacology.* (2, 1944)

Coman, Dale R., M.D. McManes Laboratory of Pathology, University of Pennsylvania School of Medicine, Philadelphia. *Assistant Professor of Pathology.* (4, 1939)

Comroe, Julius H., Jr., M.D.* University of Pennsylvania Medical School, Philadelphia. *Assistant Professor of Pharmacology.* (1, 1943; 3, 1939)

Conant, James B., Ph.D. 5 University Hall, Cambridge, Mass. *President, Harvard University; Member, National Academy of Sciences.* (2, 1932)

Concepcion, Isabelo, M.D. College of Medicine and Surgery, Manila, P.I. *Professor of Physiology, University of the Philippines.* (1, 1919)

Conklin, Ruth E., M.S., Ph.D. Vassar College. Poughkeepsie, N. Y. *Professor of Physiology.* (1, 1940)

Conn, Jerome W., M.D. University Hospital, Ann Arbor, Mich. *Assistant Professor of Internal Medicine and Research Associate in Nutrition.* (5, 1942)

Cook, Donald Hunter, Ph.D. School of Tropical Medicine of Columbia University, San Juan, Puerto Rico. *Associate Professor of Chemistry.* (2, 1929)

Cooke, Robert A., A.M., Sc.D. (hon.), M.D. 60 E. 58th St., New York City. *Director, Department of Allergy, Roosevelt Hospital.* (6, 1920)

Cooley, Thomas B., M.S., M.D. 7840 Van Dyke Pl., Detroit, Mich. *Chairman of Staff, Children's Hospital of Michigan, Detroit.* (5, 1935)

Coolidge, Thomas B., M.D., Ph.D. Abbot Hall, University of Chicago, Chicago, Ill. *Associate Professor of Biochemistry.* (2, 1942)

Coon, Julius M., Ph.D. University of Chicago, Chicago, Ill. *Instructor in Pharmacology.* (3, 1941)

Coons, Callie Mae, Ph.D. 1200 W. 78th St., Los Angeles, Calif. (5, 1933)

Cope, Otis M., M.D. New York Medical College, Flower and Fifth Avenue Hospitals, No. 1, E. 105th St., New York City. *Professor of Physiology and Biochemistry.* (1, 1929)

Corbin, Kendall B., M.D. University of Tennessee College of Medicine, 875 Monroe, Memphis. *Professor of Anatomy.* (1, 1941)

Corcoran, Arthur Curtis, C.M., M.D. Lilly Laboratory for Clinical Research, Indianapol

City Hospital, Indianapolis, Ind. *Member of Staff.* (1, 1940)

Corey, Edward Lyman, Ph.D. School of Medicine, University of Virginia, University. *Assistant Professor of Physiology.* (1, 1931)

Cori, Carl F., M.D. Washington University School of Medicine, Kingshighway and Euclid Ave., St. Louis, Mo. *Professor of Pharmacology and Biochemistry; Member, National Academy of Sciences.* (2, 1925; 3, 1934)

Cori, Gerty T., M.D. Washington University School of Medicine, St. Louis, Mo. *Research Associate Professor in Pharmacology and Biochemistry.* (2, 1927; 3, 1934)

Corley, Ralph Conner, Ph.D. Department of Chemistry, Purdue University, Lafayette, Ind. *Professor of Biochemistry.* (2, 1927)

Cornwall, Leon, M.D. 55 E. 76th St., New York City. *Attending Neurologist, N. Y. Neurological Institute.* (6, 1920)

Corper, Harry J., M.D., Ph.D. 1295 Clermont St., Denver, Colo. *Director of Research, National Jewish Hospital.* (2, 1912)

Corson, Samuel A., M.S., Ph.D.* Department of Physiology, University of Minnesota School of Medicine, Minneapolis. *Instructor in Physiology.* (1, 1943)

Corwin, Warren C., M.D. Major, M.C. AUS, Chanute Field, Ill. (4, 1940)

Co Tui, Frank, M.D. New York University College of Medicine, 477 First Ave., New York City. *Associate Professor of Experimental Surgery.* (3, 1931)

Cournard, André Frederic, M.D.* Chest Service, Bellevue Hospital, CD Building, 1st Ave. at 28th St., New York City. *Assistant Professor of Medicine, College of Physicians and Surgeons, Columbia University.* (1, 1944)

Cowgill, George Raymond, Ph.D. 333 Cedar St., New Haven, Conn. *Professor of Nutrition, Yale University.* (1, 1923; 2, 1922; 5, 1938)

Cox, Gerald J., M.S., Ph.D. 200 S. 7th Ave., LaGrange, Ill. *Research Group Leader, Corn Products Refining Co.* (2, 1930; 5, 1935)

Cox, Warren M., Jr., Ph.D. Mead Johnson & Co., Evansville, Ind. *Research Biochemist.* (2, 1935)

Craig, L. C., M.S., Ph.D. Rockefeller Institute, 66th St. and York Ave., New York City. *Associate in Chemical Pharmacology.* (2, 1938)

Crampton, E. W., Ph.D. Macdonald College, Quebec, Canada. *Associate Professor of Animal Nutrition.* (5, 1940)

Crandall, Lathan A., Jr., M.D., Ph.D. University of Tennessee College of Medicine, Memphis. *Professor of Physiology.* (1, 1930; 5, 1940)

Cressy, Norman L., M.D. Respiratory Disease Commission Laboratory, Station Hospital, Section 2, Fort Bragg, N. C. *Capt., M. C., U. S. A.; Member Commission on Acute Respiratory Diseases.* (6, 1943)

Cretcher, Leonard H., Ph.D. Mellon Institute of Industrial Research, University of Pittsburgh, Pittsburgh, Pa. *Assistant Director and Head of the Department of Research in Pure Chemistry.* (2, 1930)

Crider, Joseph O., M.D. Jefferson Medical College, Philadelphia, Pa. *Associate Professor of Physiology and Assistant Dean.* (1, 1935)

Crisler, George R., Ph.D., M.D. 33d Altitude Training Unit, Santa Ana Army Air Base, Santa Ana, Calif. *Captain, Medical Corps.* (1, 1930)

Crismon, Jefferson Martineau, M.D.* Stanford University, Calif. *Assistant Professor of Physiology.* (1, 1944)

Crittenden, Phoebe J., M.S., Ph.D. Merck Institute for Therapeutic Research, Rahway, N. J. (1, 1937; 3, 1937)

Cromwell, Hobart W., Sc.D. Abbott Laboratories, North Chicago, Ill. *Bacteriologist.* (6, 1929)

Crozier, William J., Ph.D. Biological Laboratories, Harvard University, Cambridge, Mass. *Professor of General Physiology.* (1, 1928)

Cruickschank, Ernest W. H., M.D., D.Sc., Ph.D. M.R.C.P., F.R.S.E. Marischal College, University of Aberdeen, Aberdeen, Scotland. *Professor of Physiology.* (1, 1931)

Csonka, F. A., Ph.D. Bureau of Human Nutrition and Home Economics, U. S. Department of Agriculture, Beltsville, Md. *Senior Chemist.* (2, 1924)

Cullen, Stuart C., M.D. University Hospitals, Iowa City, Iowa. *Assistant Professor of Surgery-Anesthesia.* (3, 1944)

Culler, Elmer A. K., Ph.D. University of Rochester, Rochester, N. Y. *Professor of Psychology and Director of the Laboratory.* (1, 1936)

Cunningham, Raymond W., M.S., Ph.D. Lederle Laboratories, Inc., Pearl River, N. Y. *Head, Pharmacology Research.* (3, 1941)

Cunningham, Robert Sydney, A.M., M.D., Sc.D. Albany Medical College, Albany, N. Y. *Professor of Anatomy and Dean.* (1, 1923)

Curnen, Edward C., M.D. Hospital of Rockefeller Institute, 66th St. and York Ave., New York City. *Assistant Resident Physician, Hospital of The Rockefeller Institute; Assistant, Rockefeller Institute; Lieut. (j.g.) M.C. V(S) U.S.N.R. on active duty.* (6, 1941)

Curtis, George Morris, M.A., Ph.D., M.D. Kinsman Hall, Ohio State University, Columbus. *Professor of Surgery; Chairman, Department of Research Surgery.* (1, 1933; 4, 1933)

Curtis, Howard J., M.A., Ph.D. College of Physicians and Surgeons, 630 W. 168th St., New York City. *Assistant Professor of Physiology.* (1, 1940)

Cutler, Elliott C., M.D. Peter Bent Brigham Hospital, Boston, Mass. *Moseley Professor of Surgery, Harvard Medical School; Surgeon-in-Chief, Peter Bent Brigham Hospital.* (4, 1927)

Cutting, Reginald A., M.D., Ph.D. Georgetown University School of Medicine, 3900 Reservoir Road, N.W., Washington, D. C. *Professor of Physiology and Director of the Department.* (1, 1939)

Cutting, Windsor C., M.D. Stanford University School of Medicine, San Francisco, Calif. *Assistant Professor of Therapeutics.* (3, 1939)

Daft, Floyd Shelton, Ph.D. National Institute of Health, Washington, D. C. *Senior Biochemist.* (5, 1941)

Daggs, Ray Gilbert, Ph.D. 4216 Southwestern Rd., Dallas, Texas. *Lt. Col. Hdqtrs. 8th Service Command Surgeon's Office.* (1, 1935; 5, 1933)

Dakin, Henry D., D.Sc., LL.D., Ph.D., F.I.C., F.R.S. Scarborough-on-Hudson, N. Y. (2, 1906)

Dalton, Albert J., M.A., Ph.D. National Institute of Health, Bethesda, Md. *Cytologist.* (4, 1942)

Dam, Henrik, D.Sc. University of Rochester, School of Medicine and Dentistry, 260 Crittenden Blvd., Rochester, N. Y. *Senior Research Associate in Biochemistry.* (2, 1944; 5, 1943)

D'Amour, Fred E., M.S., Ph.D. 2311 S. Josephine St., Denver, Colo. *Associate Professor, Department of Zoology, University of Denver.* (1, 1934)

D'Amour, Marie C., Ph.D., M.D. Las Encinas Sanatorium, Pasadena, Calif. *Resident Physician.* (1, 1934)

Daniels, Amy L., Ph.D. College Highway, Avon, Conn. *Retired.* (2, 1919; 5, 1933)

Danielson, Irvin S., Ph.D. Pearl River Apartments, Apt. 3H, Pearl River, N. Y. *Research Chemist.* (2, 1937)

Dann, W. J., Ph.D., D.Sc. Box 3205, Duke Hospital, Durham, N. C. *Associate Professor of Physiology.* (2, 1937; 5, 1938)

Darling, Robert Croly, M.D.* 25 Hammond St., Cambridge, Mass. *Assistant Professor of Industrial Physiology, Harvard University.* (1, 1944)

Darrow, Chester W., Ph.D. Institute for Juvenile Research, 907 S. Wolcott St., Chicago, Ill. *Research Psychologist, Institute for Juvenile Research; Associate in Physiology, University of Illinois College of Medicine.* (1, 1937)

Darrow, Daniel Cady, M.D. New Haven Hospital, New Haven, Conn. *Associate Professor of Pediatrics, Yale University.* (2, 1936)

Davenport, Horace Willard, B.Sc. (Oxon.) Ph.D. Dept. of Physiology, Harvard Medical School, 25 Shattuck St., Boston, Mass. *Instructor in Physiology.* (1, 1942)

David, Norman Austin, M.D. University of Oregon Medical School, Portland. *Professor of Pharmacology.* (3, 1934)

Davidsohn, Israel, M.D. Mount Sinai Hospital, 2750 W. 15th Place, Chicago, Ill. *Pathologist and Director of Laboratories, Mt. Sinai Hospital; Associate Professor of Pathology, College of Medicine, University of Illinois.* (4, 1939; 6, 1929)

Davis, George Kelso, Ph.D. Nutrition Laboratory, Animal Industry Dept., Agricultural Experiment Station, Gainesville, Fla. *Nutritional Technologist and Biochemist, Univ. of Florida, Florida Agricultural Experiment Station.* (5, 1944)

Davis, Hallowell, M.D. Harvard Medical School, Boston, Mass. *Associate Professor of Physiology.* (1, 1925)

Davis, Harry A., M.D., C.M. Dept. of Surgery, School of Medicine, Louisiana State University, 1542 Tulane Avenue, New Orleans. *Associate Professor of Surgery.* (4, 1944)

Davis, John Emerson, M.S., Ph.D. Dept. of Physiology and Pharmacology, Univ. of Arkansas School of Medicine, Little Rock. *Associate Professor of Pharmacology.* (1, 1941; 3, 1941)

Davson, Hugh, M.Sc., D.Sc. Dalhousie University, Halifax, N.S., Canada. Experimental Station, Porton, Wilts, England. *Associate Professor of Physiology.* (1, 1941)

Dawson, James Robertson, Jr., M.D. Vanderbilt Medical School, Nashville, Tenn. *Associate Professor.* (4, 1940)

Dawson, Martin H., M.D., C.M. Presbyterian Hospital, 620 W. 168th St., New York City. *Associate Professor of Clinical Medicine.* (4, 1934)

Dawson, Percy M., M.D. Duke University Medical School, Durham, N. C. *Visiting Professor, Dept. of Physiology.* (1, 1900)

Day, Harry G., D.Sc. University of Indiana, Bloomington. *Associate Professor, Dept. of Chemistry.* (5, 1940)

Day, Paul L., M.A., Ph.D. University of Arkansas School of Medicine, Little Rock. *Professor of Physiological Chemistry.* (2, 1934; 5, 1933)

de Beer, Edwin J., Ph.D. The Wellcome Research Laboratories, Tuckahoe, N. Y. *Assistant Director of Research.* (3, 1944)

De Bodo, Richard C., M.D. 477 First Ave., New York, N. Y. *Associate Professor of Pharmacology, New York Univ. College of Medicine.* (1, 1932; 3, 1931)

DeEds, Floyd, M.A., Ph.D. 344 Santa Ana Ave., San Francisco, Calif. *Principal Pharmacologist, Western Regional Research Laboratory, 800 Buchanan St., Albany, Calif.* (2, 1937; 3, 1927)

Defandorf, James Holmes, Ph.D. Office of the Chief of the Chemical Warfare Service, Washington, D. C. *Colonel, Sn.C.* (3, 1940)

de Gara, Paul F., M.D. 200 Pinehurst Ave., New York City. *Instructor in Pathology, Cornell University Medical College.* (6, 1941)

DeGraff, Arthur C., M.D. New York University College of Medicine, New York City. *Professor of Therapeutics.* (3, 1937)

Deichmann, Wilhelm, M.Sc., Ph.D. 527 McAlpin, Cincinnati, O. *Instructor, Kettering Laboratory of Applied Physiology; Instructor in Physiology, University of Cincinnati, College of Medicine.* (3, 1941)

del Pozo, E. C., M.D.* Medellin 196, Mexico, D. F., Mexico. (1, 1943)

Dempsey, Edward W., Sc.M., Ph.D. Harvard Medical School, Boston, Mass. *Instructor in Physiology.* (1, 1940)

Derbyshire, Arthur J., Ph.D. Wayne University College of Medicine, Detroit, Mich. *Associate Professor of Physiology.* (1, 1939)

de Savitsch, Eugene, M.D. Suite 24, 1150 Connecticut Ave., Washington, D. C. *Clinical Instructor in Surgery, Georgetown University School of Medicine.* (4, 1934)

Deuel, Harry J., Jr., Ph.D. University of Southern California Medical School, Los Angeles. *Professor of Biochemistry.* (1, 1928; 2, 1924; 5, 1933)

Deulofeu, Venancio, D. Chem. Casilla Correo 2539, Buenos Aires, Argentina. *Professor of Organic Chemistry, University of Buenos Aires.* (2, 1942)

Dienes, Louis, M.D. Massachusetts General Hospital, Boston. *Bacteriologist.* (6, 1924)

Dill, David Bruce, M.A., Ph.D. 2033 Temp. Bldg. A., O.Q.M.G., Washington, D. C. *Lt. Col. Q.M.C.; Assistant for Product Analysis, Research and Development Branch O.Q.M.G.* (1, 1941; 2, 1927; 5, 1936)

Dille, James M., M.S., Ph.D. University of Illinois School of Medicine, 1853 Polk St., Chicago. (3, 1939)

Dillon, Robert T., M.S., Ph.D. % G. D. Searle and Co., Box 5110, Chicago 80, Ill. *Head, Analytical Division.* (2, 1934)

Dingle, John H., Sc.D., M.D. Respiratory Diseases Comm. Lab., Station Hospital, Section 2, Fort Bragg, N. C. (6, 1941)

DiPalma, Joseph R., M.D.* 40-12 76th St., Jackson Heights, L. I. (1, 1943)

Dische, Zacharias, M.D. Dept. of Biochemistry, College of Physicians and Surgeons, 630 W. 168th St., New York City. (2, 1944)

Dixon, Harold M., M.D. University of Pennsylvania, Philadelphia. *Associate in Pathology; Chief of the Division of Pathology, Philadelphia General Hospital.* (4, 1936)

Doan, Charles A., M.D. Ohio State University, College of Medicine, Columbus. *Professor and Chairman of the Department of Medicine; Director of Medical Research.* (4, 1928)

Dochez, A. Raymond, M.D., Sc.D. (hon.). Presbyterian Hospital, 620 W. 168th St., New York City. *John E. Borne Professor of Medical and Surgical Research, Columbia University; Member of National Academy of Sciences.* (4, prior to 1920; 6, 1922)

Dohan, F. Curtis, M.D. 80 Princeton Rd., Cynwyd, Pa. *Fellow, George S. Cox Medical Research Institute; Associate in Medicine, University of Pennsylvania, Philadelphia.* (1, 1941)

Doisy, Edward A., M.S., Ph.D., Sc.D. St. Louis University School of Medicine, St. Louis 4, Mo. *Professor of Biological Chemistry; Member, National Academy of Sciences.* (2, 1920)

Dominguez, Rafael, M.D. Saint Luke's Hospital, 11311 Shaker Blvd., Cleveland, O. *Director of Laboratories, St. Luke's Hospital; Associate in Pathology, Western Reserve University.* (1, 1935)

Donahue, D. D., D.Sc. Division of Industrial Hygiene, National Institute of Health, Bethesda, Md. *Physiologist, Toxicology Section, Division of Industrial Hygiene, U. S. Public Health Service.* (3, 1941)

Dooley, M. S., M.D. 766 Irving Ave., Syracuse, N. Y. *Professor of Pharmacology, College of Medicine, Syracuse University.* (3, 1923)

Dorfman, Ralph I., Ph.D. Dept. of Biochemistry, Western Reserve University School of Medicine, Cleveland, O. *Assistant Professor of Biochemistry.* (2, 1940)

Dotti, Louis Basil, M.A., Ph.D. St. Luke's Hospital, Amsterdam Ave. and 113th St., New York City. *Chemist, St. Luke's Hospital; Associate in Physiology and Biochemistry, New York Medical College, Flower and Fifth Avenue Hospital, New York, N. Y.* (1, 1937)

Doty, J. Roy, Ph.D. American Dental Association Bureau of Chemistry, 222 E. Superior St., Chicago, Ill. *Associate Chemist.* (2, 1941)

Dounce, Alexander L., Ph.D. Strong Memorial Hospital, 260 Crittenden Blvd., Rochester, N. Y. *Instructor in Biochemistry, University of Rochester, School of Medicine and Dentistry.* (2, 1944)

Dow, Philip, Ph.D. University of Georgia School of Medicine, Augusta. *Associate Professor of Physiology.* (1, 1939)

Dow, Robert S., M.D., Ph.D. University of Oregon Medical School, Portland. *Associate Professor of Anatomy.* (1, 1940)

Downs, Ardrey W., M.A., M.D., D.Sc., F.A.C.P. University of Alberta, Edmonton, Canada. *Professor of Physiology and Pharmacology.* (1, 1917)

Downs, Cora M., Ph.D. 1625 Alabama St., Lawrence, Kan. (6, 1929)

Drabkin, David L., M.D. Medical School, University of Pennsylvania, Philadelphia. *Associate Professor of Physiological Chemistry.* (2, 1928; 5, 1934)

Dragstedt, Carl A., Ph.D., M.D. Northwestern University Medical School, 303 E. Chicago Ave., Chicago, Ill. *Professor of Pharmacology.* (1, 1928; 3, 1932)

Dragstedt, Lester R., M.D., Ph.D. University of Chicago, Chicago, Ill. *Professor of Surgery.* (1, 1920)

Draize, J. H., Ph.D. Division of Pharmacology, Food & Drug Administration, U. S. Dept. of Agriculture, Washington, D. C. *Pharmacologist.* (3, 1940)

Drake, T. G. H., M.B., F.R.C.P. (c). University of Toronto, Toronto, Canada. *Junior Demonstrator in Paediatrics, Department of Medicine, University of Toronto; Clinical Assistant on Active Staff and Associate Director Research Laboratory, Hospital for Sick Children.* (5, 1936)

Draper, William B., M.Sc., M.D. University of Colorado School of Medicine, 4200 E. 9th Ave., Denver. *Associate Professor of Physiology and Pharmacology.* (3, 1938)

Dresbach, Melvin, M.S., M.D. Hahnemann Medical College, Philadelphia, Pa. *Visiting Fellow in Physiology.* (1, 1912)

Dreyer, Nicholas Bernard, M.A. (Oxon). Long Island College of Medicine, 350 Henry St., Brooklyn, N. Y. *Associate Professor of Physiology and Pharmacology.* (3, 1942)

Drill, Victor Alexander,* Ph.D. Dept. of Pharmacology, Yale University School of Medicine, 333 Cedar St., New Haven, Conn. *Instructor in Pharmacology.* (1, 1943)

Drinker, Cecil K., M.D. Harvard University School of Public Health, Boston, Mass. *Professor of Physiology and Dean.* (1, 1915)

Drinker, Katherine R., M.D. Harvard School of Public Health, 55 Shattuck St., Boston, Mass. *Instructor in Public Health.* (1, 1915)

Drury, Douglas R., M.D. University of Southern California, Los Angeles. *Professor of Physiology.* (1, 1932)

Dubin, Harry E., Ph.D. 250 E. 43rd St., New York City. *President, H. E. Dubin Laboratories, Inc.* (2, 1925)

DuBois, Eugene F., M.D. Cornell University Medical School, 1300 York Ave., New York, N. Y. *Professor and Head of the Department of Physiology and Biophysics; Attending Physician, New York Hospital; Member, National Academy of Sciences; Captain (M.C.) U.S.N.R.* (1, 1913; 3, 1921; 5, 1935)

Dubos, Rene J., Ph.D., D.Sc. Rockefeller Institute for Medical Research, 66th St. and York Ave., New York City. *Member.* (6, 1938)

Dukes, H. H., D.V.M., M.S. New York State Veterinary College, Cornell University, Ithaca, N. Y. *Professor of Veterinary Physiology.* (1, 1934)

Dulaney, Anna D., A.M., Ph.D. Pathological Institute, University of Tennessee, Memphis. *Assistant Professor of Bacteriology, Medical School.* (6, 1924)

Dumke, Paul Rudolph, M.D. Clinical Research Section, Medical Research Lab., Edgewood Arsenal, Edgewood, Md. *Instructor in Pharmacology, University of Pennsylvania; Captain, M.C.* (3, 1942)

Dunlap, Charles E., M.D. Tulane University of Louisiana, 1430 Tulane Ave. New Orleans. *Associate Professor of Pathology.* (4, 1942)

Dunn, Max Shaw, Ph.D. University of California, Los Angeles. *Professor of Chemistry.* (2, 1933)

Durrant, Edwin Poe, M.A., Ph.D. Ohio State University, Columbus. *Associate Professor of Physiology.* (1, 1928)

Dutcher, R. Adams, M.S., M.A., D.Sc. Pennsylvania State College, State College. *Professor and Head of Department of Agricultural Biochemistry.* (2, 1920; 5, 1933)

Duval, Charles Warren, M.D. Tulane University, New Orleans, La. *Professor Emeritus of Pathology and Bacteriology.* (4, 1913)

du Vigneaud, Vincent, M.S., Ph.D. Cornell University Medical College, 1300 York Ave., New York 21, N. Y. *Professor of Biochemistry; Member National Academy of Sciences.* (2, 1929; 5, 1934)

Dworkin, Simon, D.D.S., M.D., C.M. Biology Building, McGill University, Montreal, Quebec, Canada. *Lecturer in Physiology, Faculty of Medicine.* (1, 1931)

Dye, J. A., Ph.D. James Law Hall, Cornell University, Ithaca, N. Y. *Associate Professor of Physiology.* (1, 1929)

Dye, Marie, M.S., Ph.D. Michigan State College, East Lansing. *Dean of Division of Home Economics.* (2, 1929; 5, 1933)

Dyer, Helen M., M.S., Ph.D. National Cancer Institute, U.S.P.H.S., Bethesda, Md. *Research Associate.* (2, 1936; 5, 1937)

Eadie, George S., Ph.D. Duke University School of Medicine, Box 3709, Durham, N. C. *Professor of Physiology and Pharmacology.* (1, 1929; 3, 1940)

Eagle, Harry, M.D. Johns Hopkins Hospital, Baltimore, Md. *Passed Assistant Surgeon, U. S. Public Health Service; Lecturer in Medicine, Johns Hopkins University Medical School.* (4, 1936)

Earle, Wilton R., Ph.D. U. S. Public Health Service, National Cancer Institute, Bethesda, Md. *Senior Cytologist.* (4, 1940)

Eaton, Alonzo Guy, M.A., Ph.D. Louisiana State University Medical Center, New Orleans. *Associate Professor of Physiology.* (1, 1933)

Eaton, Monroe D., M.D. State Department of Public Health, Influenza Laboratory, 1392 University Ave., Berkeley, Calif. *Staff Member, International Health Division of The Rockefeller Foundation.* (6, 1937)

Ecker, E. E., Ph.D. School of Medicine, Western Reserve University, 2085 Adelbert Rd., Cleveland, O. *Professor of Immunology.* (4, 1925)

Eckstein, Henry C., M.S., Ph.D. 320 W. Medical Building, University of Michigan, Ann Arbor. *Associate Professor of Biological Chemistry.* (2, 1925)

Eddy, Nathan B., M.D. National Institute of Health, Bethesda, Md. *Principal Pharmacologist, United States Public Health Service.* (1, 1919; 3, 1929)

Eddy, Walter H., A.M., Ph.D. 60 E. 42nd St., New York, N. Y. *Professor Emeritus, Physiological Chemistry, Teachers College, Columbia University.* (2, 1913; 5, 1933)

Edsall, Geoffrey, M.D. Antitoxin and Vaccine Laboratory, 375 South St., Jamaica Plain, Mass. *Acting Director, Division of Biologic Laboratories, Massachusetts Department of Public Health; Associate in Public Health Laboratory Methods, Simmons College; Instructor in Applied Immunology, Harvard School of Public Health.* (6, 1943)

Edsall, John Tileston, M.D. Harvard Medical School, Boston, Mass. *Associate Professor of Biological Chemistry and Tutor in Biochemical Sciences.* (2, 1931).

Edwards, Dayton J., Ph.D. 1300 York Ave., New York City. *Associate Professor of Physiology; Assistant Dean, Cornell University Medical College.* (1, 1921)

Edwards, Jesse E., M.D. 25 Edgehill Rd., Brookline, Mass. (4, 1941)

Edwards, J. Graham, A.M., Ph.D. 24 High St., Buffalo, N. Y. *Assistant Professor of Anatomy, University of Buffalo.* (1, 1932)

Eggerth, Arnold H., Ph.D. Hoagland Laboratory, 335 Henry St., Brooklyn, N. Y. *Associate Professor of Bacteriology, Long Island College of Medicine.* (4, 1925)

Ehrenstein, Maximilian R., Ph.D. 806 Maloney Clinic, University of Pennsylvania Hospital, 36th and Spruce Sts., Philadelphia. *Assistant Professor of Chemistry assigned to Medicine.* (2, 1942)

Eichelberger, Lillian, Ph.D. University of Chicago, Dept. of Medicine, Chicago, Ill. *Assistant Professor of Biochemistry.* (2, 1937)

Eiseman, Anna J., Ph.D. U. S. Public Health Service Hospital, Lexington, Ky. *Biological Chemist.* (2, 1930)

Elderfield, Robert C., Ph.D. Columbia University, New York City. *Professor of Chemistry.* (2, 1934)

Elftman, Herbert, M.A., Ph.D. College of Physicians and Surgeons, Columbia University, 630 W. 168th St., New York City. *Assistant Professor in Anatomy.* (1, 1940)

Eliot, Martha M., M.D. United States Children's Bureau, Washington, D. C. *Assistant Chief.* (5, 1933)

Elliott, K. Allan C., M.Sc., Ph.D. Montreal Neurological Institute, 3801 University St., Montreal, Canada. (2, 1937)

Ellis, Frederick W., M.D. Monson, Mass. (1, 1887)

Ellis, Lillian N., Ph.D. Adelphi College, Garden City, N. Y. (5, 1940)

Ellis, Max Mapes, A.M., Ph.D., Sc.D. University of Missouri, Columbia. *Professor of Physiology and Pharmacology.* (1, 1923)

Ellis, N. R., M.S. Bureau of Animal Industry, U. S. Department of Agriculture, Beltsville Research Center, Beltsville, Md. *Principal Chemist, Animal Nutrition Division.* (2, 1928; 5, 1933)

Elser, William J., M.D. 1300 York Ave., New York City. *Emeritus Professor of Applied Pathology and Bacteriology, New York Hospital.* (6, 1920)

Elvehjem, Conrad Arnold, M.S., Ph.D., Sc.D. Biochemistry Building, University of Wisconsin, Madison. *Professor of Biochemistry; Member, National Academy of Sciences.* (2, 1931; 5, 1933)

Emerson, George A., M.S., Ph.D. University of Texas, Medical Branch, Galveston. *Professor of Pharmacology.* (3, 1935)

Emerson, Gladys A., Ph.D. Merck Institute of Therapeutic Research, Rahway, N. J. *Nutritionist.* (5, 1942)

Emerson, Oliver H., Ph.D. Western Regional Research Laboratory, U. S. Dept. of Agriculture, Albany 6, Calif. *Associate Chemist.* (2, 1938)

Emery, Frederick E., D.V.M., M.S., Ph.D. University of Buffalo Medical School, Buffalo, N. Y. *Assistant Professor of Physiology.* (1, 1930)

Emmett, Arthur D., M.A., Ph.D. Research Department, Parke, Davis & Co., Detroit, Mich. *Assistant Director of Research.* (2, 1908; 5, 1933)

Enders, John F., A.M., Ph.D. Department of Bacteriology, Medical School, Harvard University, Boston, Mass. *Assistant Professor of Bacteriology and Immunology.* (6, 1936)

Engle, Earl Theron, Ph.D. College of Physicians and Surgeons, Columbia University, 630 W. 168th St., New York City. *Professor of Anatomy.* (1, 1930)

Epstein, Albert A., M.D. 1111 Madison Ave., New York City. *Physician, Beth Israel Hos-*

pital; Physician, Hospital for Joint Diseases. (2, 1912)

Erickson, Cyrus C., M.D. Duke University School of Medicine, Durham, N. C. *Associate in Pathology.* (4, 1941)

Erlanger, Joseph, M.D., LL.D., Sc.D. Washington University School of Medicine, 4580 Scott Ave., St. Louis, Mo. *Professor of Physiology; Member of the National Academy of Sciences.* (1, 1901)

Espe, Dwight L., Ph.D. Iowa State College, Ames. *Assistant Research Professor in Dairy Husbandry.* (1, 1940)

Essex, Hiram E., M.S., Ph.D. Mayo Foundation, Rochester, Minn. *Associate Professor of Physiology, Institute of Experimental Medicine.* (1, 1932; 3, 1940)

Ettinger, C. H., M.D., C.M., F.R.S.C.* Queen's University, Kingston, Canada. *Professor of Physiology.* (1, 1943)

Evans, Earl Alison, Jr., Ph.D. Department of Biochemistry, University of Chicago, Chicago, Ill. *Professor and Chairman of Department.* (2, 1939)

Evans, Everett Idris, M.D., Ph.D. Department of Surgery, Medical College of Virginia, Richmond. *Assistant Professor of Surgery; Responsible Investigator, Committee on Medical Research, National Research Council.* (1, 1935)

Evans, Gerald Taylor, M.D., Ph.D. University of Minnesota Hospitals, Minneapolis. *Director of Laboratory Service, University of Minnesota Hospitals; Associate Professor of Medicine, University of Minnesota.* (1, 1942)

Evans, Herbert M., M.D. University of California, Berkeley. *Professor of Anatomy and Director of Institute of Experimental Biology; Member of the National Academy of Sciences.* (1, 1919)

Evans, William E., Jr., M.S., Ph.D. University of Maryland Medical School, Baltimore. *Assistant Professor of Pharmacology.* (3, 1940)

Eveleth, D. F., Ph.D., D.V.M. North Dakota Agricultural College, Fargo. *Professor, Veterinary Science, North Dakota Agricultural Experiment Station.* (2, 1939)

Everett, Mark Reuben, Ph.D. University of Oklahoma Medical School, Oklahoma City. *Professor of Biochemistry.* (2, 1929)

Ewing, P. L., M.S., Ph.D. University of Texas School of Medicine, Galveston. *Associate Professor of Pharmacology.* (3, 1938)

Eyster, John A. English, M.D. University of Wisconsin, Madison. *Professor of Physiology.* (1, 1906; 3, 1908)

Fahr, George, M.D. 102 Millard Hall, University of Minnesota Medical School, Minneapolis. *Professor of Clinical Medicine.* (1, 1913; 3, 1940)

Failey, Crawford F., Ph.D. 416 South 6th Street, Terre Haute, Ind. Department of Pharmacology, University of Chicago. *Research Assoc., Associate Professor.* (2, 1933)

Fairhall, Lawrence T., M.A., Ph.D. U. S. Public Health Service, Washington, D. C. *Principal Industrial Toxicologist.* (2, 1924).

Falk, Carolyn R., B.A. 40 E. 66th St., New York City. *Bacteriologist, Bureau of Laboratories, New York City Dept. of Health.* (6, 1943)

Falk, K. George, Ph.D. 40 E. 66th St., New York City. *Director, Laboratory of Industrial Hygiene.* (2, 1913)

Famulener, Lemuel W., Ph.C., M.D. 275 Engle St., Englewood, N. J. (6, 1920)

Farber, Sidney, M.D. Harvard Medical School, 25 Shattuck St., Boston, Mass. *Assistant Professor of Pathology.* (4, 1934)

Farmer, Chester J., A.M. Northwestern Medical School, 303 E. Chicago Ave., Chicago, Ill. *Professor of Chemistry.* (2, 1935)

Farr, Lee E., M.D. Alfred I. duPont Institute, Wilmington, Del. *Director of Research. On leave of absence in U. S. Navy.* (4, 1941)

Farrell, James I., Ph.D., M.D. 17 Chatauqua Pl., Bradford, Pa. (1, 1938)

Fassett, David W., M.D. Department of Therapeutics, New York University College of Medicine, 414 E. 26 St., New York City. *Fellow, Department of Therapeutics.* (3, 1942)

Favorite, Grant O., M.D. 1313 Andover Rd., Overbrook, Philadelphia, Pa. *Professor of Bacteriology, Hahnemann Medical College, Philadelphia.* (6, 1943)

Fay, Marion, M.A., Ph.D. Woman's Medical College of Pennsylvania, East Falls, Philadelphia 29. *Professor of Physiological Chemistry.* (2, 1937)

Feldman, Harry A., M.D. University of Tennessee, Memphis. *Fellow (on leave) in Medicine, Harvard Medical School; Capt., AUS, Chief Div. Bact.* (6, 1943)

Feldman, William H., D.V.M., M.S. The Mayo Foundation, Rochester, Minn. *Associate in the Division of Experimental Surgery and Pathology.* (4, 1934)

Feller, Alto E., M.D. Commission on Acute Respiratory Diseases, Station Hospital, Section 2, Fort Bragg, N. C. *Consultant to Secretary of War.* (6, 1943)

Fellows, Edwin J., M.S., Ph.D. Temple University School of Medicine, Philadelphia, Pa. *Assistant Professor of Pharmacology.* (3, 1939)

Felton, Lloyd D., M.D., D.Sc. Division of Infectious Diseases, National Institute of Health, 25th and E Sts., N.W., Washington, D. C. *Senior Surgeon, United States Public Health Service.* (6, 1926)

Fenn, Wallace Osgood, A.M., Ph.D. University of Rochester School of Medicine and Dentistry, 260 Crittenden Blvd., Rochester, N. Y. *Professor of Physiology; Member, National Academy of Sciences.* (1, 1924)

Fenning, Con, M.D., M.A. University of Utah School of Medicine, Salt Lake City. *Associate Professor of Pharmacology and Physiology.* (1, 1942)

Ferguson, James Kenneth Wallace, M.A., M.D. 76 Kilbarry Rd., Toronto, Ontario, Canada. *Assistant Professor of Pharmacology, University of Toronto. Wing Commander, R.C.A.F.* (1, 1933; 3, 1941)

Ferguson, John Howard, M.D., M.A., L.M.S.S.A. Dept. of Physiology, School of Medicine, University of North Carolina, Chapel Hill. *Professor of Physiology and Acting Professor of Pharmacology.* (1, 1933; 3, 1939)

Ferguson, L. Kraeer, M.D. 133 S. 36th St. Philadelphia, Pa. *Assistant Professor of Surgery, University of Pennsylvania; Surgeon, Philadelphia General Hospital; Assistant Surgeon, University of Pennsylvania Hospital.* (4, 1935)

Ferry, John Douglass, Ph.D. Department of Physical Chemistry, Harvard Medical School, 25 Shattuck St., Boston, Mass. *Research Associate.* (2, 1941)

Ferry, Newell S., M.D., Parke, & Davis Co. Detroit, Mich. *Assistant Director of Research.* (6, 1916)

Ferry, Ronald M., M.D. 966 Memorial Drive, Cambridge, Mass. *Master of John Winthrop House.* (2, 1924)

Fetcher, Edwin S., Jr., Ph.D.* 1800 Shroyer Road, Dayton, Ohio. *Special Consultant to the Army Air Forces, AAF Materiel Command, Wright Field.* (1, 1944)

Fetter, Dorothy, Ph.D.* Department of Hygiene, Brooklyn College, Brooklyn, N. Y. *Instructor in Physiology.* (1, 1944)

Fevold, Harry L., M.S., Ph.D. Western Regional Research Laboratory, Albany 6, Calif. *Senior Biochemist.* (2, 1942)

Field, John, II, A.M., Ph.D. Stanford University, Stanford, Calif. *Professor of Physiology.* (1, 1930)

Fincke, Margaret L., Ph.D. Oregon State College, Corvallis. *Associate Professor of Foods and Nutrition, School of Home Economics.* (5, 1940)

Findley, Thomas, Jr., M.D. Ochsner Clinic, 3503 Prytania, New Orleans, La. *Head of the Department of Internal Medicine, Ochsner Clinic, New Orleans; Assistant Professor of Clinical Medicine, Tulane University School of Medicine.* (1, 1938)

Fine, Morris S., Ph.D. Central Laboratories, General Foods Corporation, Hoboken, N. J. *Director of Research.* (2, 1912; 5, 1933)

Finland, Maxwell, B.S. Boston City Hospital, Boston, Mass. *Assistant Professor of Medicine, Harvard Medical School.* (6, 1941)

Firor, Warfield Monroe, M.D. Johns Hopkins Hospital, Baltimore, Md. *Associate Professor of Surgery, Johns Hopkins University.* (1, 1932)

Fischer, Ernst, M.D., Dr. habil. Medical College of Virginia, Richmond. *Associate Professor of Physiology and Pharmacology.* (1, 1936)

Fischer, Hermann O. L., Ph.D. Banting Institute, 100 College St., University of Toronto, Toronto 5, Canada. *Research Professor of Organic Chemistry.* (2, 1940)

Fischer, Martin H., M.D., Pharm. D. (hon.), Sc.D. University of Cincinnati College of Medicine, Eden Ave., Cincinnati 19, O. *Professor of Physiology.* (1, 1901; 2, 1919)

Fishberg, Ella H., M.A., M.D. Beth Israel Hospital, Stuyvesant Park East, New York City. *Biochemist.* (2, 1931)

Fisher, Albert Madden, M.A., Ph.D. Connaught Laboratories, University of Toronto, Toronto, Canada. *Research Associate.* (2, 1944)

Fisher, Kenneth C., M.A., Ph.D. University of Toronto, Toronto, Ont., Canada. *Assistant Professor of Physiological Zoology.* (1, 1940)

Fiske, Cyrus H., M.D. Harvard Medical School, Boston, Mass. *Professor of Biological Chemistry.* (2, 1914)

Fitzgerald, Mabel P., 54 A, George Sq., Edinburgh, Scotland. (1, 1913)

Fitzhugh, O. Garth, Ph.D. Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington, D. C. *Pharmacologist.* (3, 1940)

Fleischmann, Walter, M.D., Ph.D. Harriet Lane Home, Johns Hopkins Hospital, Baltimore, Md. *Associate in Pediatrics, Johns Hopkins University.* (1, 1940)

Fleisher, Moyer S., M.D. Jewish Hospital, St. Louis, Mo. *Research Bacteriologist.* (4, 1924; 6, 1932)

Flexner, Louis B., M.D. Department of Embryology, Carnegie Institution of Washington, Wolfe and Madison Sts., Baltimore, Md. *Research Associate.* (1, 1933)

Flock, Eunice V., Ph.D. Mayo Clinic, Rochester, Minn. *Assistant Professor of Biochemistry, University of Minnesota; Associate in the Division of Experimental Medicine, The Mayo Foundation.* (2, 1940)

Florman, Alfred L., M.D. 9th Service Command Laboratory, Presidio of Monterey, Calif. *Lieut., M. C.* (6, 1942)

Flosdorf, Earl W., Ph.D. Forest Grove, Bucks Co., Pa. *Research—University of Pennsylvania School of Medicine.* (6, 1941)

Floyd, Cleveland, M.D., Sc.D. 246 Marlborough St., Boston, Mass. *Chief Examiner, Boston Health Dept.* (6, 1916)

Foa, Piero Pio, Ph.D.* 710 S. Wolcott St., Chicago, Ill. *Assistant Professor of Physiology, Chicago Medical School.* (1, 1944)

Folch, Jordi, M.D. Rockefeller Institute for Medical Research, New York City. *Associate.* (2, 1941)

Follensby, Edna M., Ph.G. 80 E. Concord St., Boston, Mass. *Research Assistant, Evans Memorial.* (6, 1933)

Follis, Richard H., Jr., M.D. Major, M.C. A.U.S. Hq. AAF., Office of Flying Safety, Winston Salem, N. C. *Associate in Pathology, Harvard University (on leave of absence).* (4, 1942)

Foot, Nathan Chandler, M.D. 340 E. 72nd St., New York City. *Professor of Surgical Pathology, Cornell University Medical College; Surgical Pathologist, New York Hospital.* (4, 1924)

Forbes, Alexander, A. M., M.D. Harvard Medical School, Boston, Mass. *Professor of Physiology; Member of the National Academy of Sciences.* (1, 1910)

Forbes, Ernest B., Ph.D. State College, Pa. *Director of the Institute of Animal Nutrition.* (1, 1917; 5, 1935)

Forbes, Henry S., M.D. Forest St., Milton, Mass. *Associate in Neuropathology, Harvard Medical School.* (1, 1931)

Forbes, John C., M.A., Ph.D. Medical College of Virginia, Richmond. *Associate Professor of Biochemistry.* (2, 1937)

Forbes, William H., M.A., Ph.D.* Harvard University, Fatigue Laboratory, Boston, Mass. *Research Fellow, Assistant Director of Fatigue Lab., Assistant Professor of Industrial Physiology.* (1, 1943)

Fosdick, Leonard S., Ph.D. 311 E. Chicago Ave., Chicago, Ill. *Professor of Chemistry, Northwestern University.* (2, 1944)

Foster, G. L., Ph.D. College of Physicians and Surgeons, 630 W. 168th St., New York City. *Associate Professor of Biological Chemistry.* (2, 1923)

Foster, Harry E., M.D. Cutter Laboratory, Berkeley, Calif. *Medical Director.* (6, 1913)

Foster, Robert H. K., Ph.D., M.D. 19 Brookfield Ave., Nutley, N. J. *Chief Pharmacologist, Hoffman-La Roche, Inc.* (1, 1940; 3, 1944)

Foster, Ruth A. C., Ph.D. Dept. of Botany and Bacteriology, University of Texas, Austin. *Instructor.* (6, 1943)

Fothergill, LeRoy D., M.D. Naval Medical Center, Bethesda, Md. *Assistant Professor of Bacteriology and Immunology, Harvard Medical School. Now serving as Lt. Comdr. M. C., U. S. Naval Reserve.* (6, 1936)

Fraenkel-Conrat, Heinz, M.D., Ph.D. Western Regional Research Laboratory, Protein Division, Albany 6, Calif. *Associate Research Chemist.* (2, (1942)

Francis, Thomas, Jr., M.D., M.S., Sc.D. (hon.). School of Public Health, University of Michigan, Ann Arbor. *Professor of Epidemiology.* (4, 1940; 6, 1930)

Franke, Florent E., M.D. 9 Sylvester, Webster Groves, Mo. *Assistant Professor of Physiology, St. Louis University School of Medicine.* (1, 1934)

Frankel, Edward M., Ph.D. 214 River Rd., Nyack, N. Y. *President, Supreme Liquors, Inc.* (2, 1916)

Fraser, Alexander MacLeod, A.M., M.D., C.M. McGill University, Montreal, Canada. *Lecturer in Pharmacology.* (3, 1939)

Fraser, Donald T., M.B. Connaught Laboratories, University of Toronto, Toronto 5, Canada. *Professor of Hygiene and Preventive Medicine.* (6, 1935)

Free, Alfred H. School of Medicine, Western Reserve University, Cleveland, O. *Asst. Professor of Biochemistry.* (5, 1944)

Freeman, Harry, M.D. Worcester State Hospital, Worcester, Mass. *Internist, Research Service.* (1, 1939)

Freeman, Leslie Willard, Ph.D., M.D.* 660 E. Groveland Park, Chicago, Ill. *Resident, Chicago Memorial Hospital.* (1, 1944)

Freeman, Norman, E., M.D. University of Pennsylvania Medical School, Philadelphia. *J. Wm. White Assistant Professor of Research Surgery.* (1, 1936)

Freeman, Smith, M.D., Ph.D. Northwestern University School of Medicine, 303 E. Chicago Ave., Chicago, Ill. *Assistant Professor of Physiology and Pharmacology.* (1, 1937)

Freund, Jules, M.D. Public Health Research Institute of the City of New York, Foot of E. 15th St., New York, N. Y. *Member.* (4, 1930; 6, 1924)

Friedemann, Theodore E., M.A., Ph.D. Northwestern University Medical School, 303 E. Chicago Ave., Chicago, Ill. *Associate Professor of Physiology.* (2, 1925)

Friedemann, Ulrich, M.D. Department of Bacteriology, The Jewish Hospital of Brooklyn, Classon and St. Marks Ave., Brooklyn, N. Y. (6, 1938)

Friedewald, William F., M.D. International Health Division, The Rockefeller Foundation, 66th St. and York Ave., New York City. *Member of Staff.* (4, 1941)

Friedgood, Harry B., M.D. Harvard Medical School, Boston, Mass. *Instructor in Medicine.* (1, 1936)

Friedman, Maurice H., Ph.D., M.D. Hunter Field Regional Hospital, Hunter Field, Ga. *Captain (MC) AUS, Chief, Gastro-enterology.* (1, 1929)

Friedman, M. H. F., M.A., Ph.D. Jefferson Medical College of Philadelphia, 1025 Walnut St., Philadelphia, Pa. *Assistant Professor of Physiology.* (1, 1941)

Friedman, Nathan B., M.D. Stanford University School of Medicine, San Francisco, Calif. *Instructor in Pathology.* Army Medical Museum, 7th & Independence, Washington, D. C. (4, 1942)

Frisch, Arthur W., Ph.D., M.D. College of Medicine, Wayne University, Detroit, Mich. *Instructor.* (6, 1938)

Fruton, J. S., Ph.D. Rockefeller Institute, 66th St. and York Ave., New York City. *Associate in Chemistry.* (2, 1938)

Fuge, Nicholas W., M.S., Ph.D. State University of Iowa, Medical School, Iowa City. *Instructor in Pharmacology, on leave.* (3, 1944)

Fulton, John Farquhar, M.A., Ph.D., M.D. Yale University School of Medicine, New Haven, Conn. *Sterling Professor of Physiology.* (1, 1925)

Funk, Casimir, D.Sc., Ph.D. 186 Riverside Drive, New York 24, N. Y. (2, 1921)

Furth, Jacob, M.D. Cornell University Medical College, 1300 York Ave., New York City. *Associate Professor of Pathology.* (4, 1932; 6, 1930)

Gaebler, Oliver H., Ph.D., M.D. Henry Ford Hospital, Detroit, Mich. *Associate in Chemistry.* (2, 1927)

Gaffron, Hans, Ph.D. Chemical Department, University of Chicago, Chicago, Ill. *Research Associate (Assistant Professor).* (2, 1941)

Gagge, Adolf Pharo, Ph.D. Aeromedical Research Laboratory, Wright Field, Dayton, O. *Lt. Col.; Chief, Biophysics Branch, Air Corps, U. S. Army; on leave from Yale University and John B. Pierce Laboratory of Hygiene.* (1, 1939)

Galambos, Robert, M.A., PhD. University of Rochester School of Medicine and Dentistry, 260 Crittenden Blvd., Rochester, N. Y. (1, 1942)

Gall, Edward A., M.D. Bethesda Hospital, Cincinnati, O. *Assistant Professor of Pathology, College of Medicine, University of Cincinnati.* (4, 1941)

Gallagher, Thomas F., Ph.D. University of Chicago, Chicago, Ill. *Associate Professor of Biochemistry.* (2, 1932)

Gallup, Willis D., M.S., Ph.D. Oklahoma Agricultural and Mechanical College, Stillwater. *Chemist and Professor of Agricultural Chemistry.* (2, 1932)

Gamble, James L., M.D., S.M. 33 Edgehill Rd., Brookline, Mass. *Professor of Pediatrics, Harvard Medical School.* (2, 1922; 5, 1933)

Gantt, W. Horsley, M.D. Phipps Psychiatric Clinic, Johns Hopkins Hospital, Baltimore, Md. *Associate in Psychiatry.* (1, 1935)

Garbat, Abraham L., M.D. 103 E. 78th St., New York City. *Attending Physician, Lenox Hill Hospital.* (6, 1913)

Gardner, Leroy U., M.D. Saranac Laboratory for Study of Tuberculosis, Saranac Lake, N. Y. *Director of the Trudeau Foundation.* (4, 1927)

Garrey, Walter Eugene, Ph.D., M.D. Vanderbilt University School of Medicine, Nashville, Tenn. *Professor of Physiology.* (1, 1910; 2, 1906)

Gasser, Herbert S., A.M., M.D., Sc.D. (hon.) Rockefeller Institute for Medical Research, 66th St. and York Ave., New York City. *Director of Laboratories; Member of the National Academy of Sciences.* (1, 1915; 3, 1924)

Gates, Olive, M.D. 25 Shattuck St., Boston, Mass. *Associate Pathologist.* (4, 1940)

Gaunt, Robert, Ph.D. Washington Square College, New York University, New York City. *Associate Professor of Biology.* (1, 1939)

Gay, Leslie N., M.D. 1114 St. Paul St., Baltimore, Md. *Director of the Allergy Clinic, Johns Hopkins Hospital; Visiting Physician to Johns Hopkins Hospital; Associate in Medicine, Johns Hopkins University.* (6, 1927)

Geiling, E. M. K., M.S., M.D., Ph.D. University of Chicago, Chicago, Ill. *Frank P. Hixon Distinguished Service Professor of Pharmacology and Chairman of Department.* (1, 1933; 2, 1927; 3, 1925)

Gelfan, Samuel, Ph.D. 212 West 72nd St., New York, N. Y. *Assistant Professor of Physiology, Columbia University College of Physicians and Surgeons.* (1, 1930)

Gellhorn, Ernst, M.D., Ph.D. Room 116, Medical Sciences, University of Minnesota, Minneapolis. *Professor of Neurophysiology.* (1, 1930)

Gemmill, Chalmers L., M.D. School of Aviation Medicine, Pensacola, Fla. *Commander, U.S.N.R.* (1, 1928; 2, 1935)

Gerard, R. W., Ph.D., M.D. University of Chicago, Chicago, Ill. *Professor of Physiology.* (1, 1927)

Gerstenberger, Henry John, M.D. Western Reserve University, Cleveland, O. *Professor of Pediatrics, School of Medicine, Western Reserve University; Director of Pediatrics, Babies and Children's Hospital.* (5, 1938)

Gesell, Robert, M.D. University of Michigan, Ann Arbor. *Professor of Physiology.* (1, 1913)

Gettler, Alexander O., A.M., Ph.D., LL.D. New York University, 29 Washington Place, New York City. *Professor of Chemistry and Toxi-*

cology; Toxicologist to Chief Medical Examiner's Office. (2, 1916)

Gey, George Otto, M.D. Cancer Research and Tissue Culture Laboratory, Johns Hopkins Medical School, Baltimore, Md. *Instructor in Surgery.* (1, 1940)

Gibbs, Frederick Andrews, M.D. Neuropsychiatric Institute, University of Illinois, 912 So. Wood St., Chicago. (1, 1935)

Gibbs, Owen Stanley, M.B., Ch.B. (Edin.) R.F.D. 4, Box 428, Memphis, Tenn. *Research Consultant.* (1, 1935; 3, 1930)

Gibson, Robert Banks, Ph.D. University Hospital, Iowa City, Iowa. *Associate Professor of Biochemistry, State University of Iowa.* (1, 1907; 2, 1906)

Gies, William John, M.S., Ph.D., Sc.D., LL.D., F.A.C.D. 632 W. 168th St., New York City. *Professor of Biological Chemistry, Columbia University.* (1, 1898; 2, 1906; 3, 1909)

Gilbert, Ruth, A.M., M.D. R.F.D. 2, Altamont, N. Y. *Bacteriologist, New York State Department of Health, Albany.* (6, 1920)

Gilman, Alfred, Ph.D. Edgewood Arsenal, Md. *Captain, Sn.C., A.U.S.* (1, 1935; 3, 1934)

Gilson, Arthur S., Jr., A.M., Ph.D. Washington University Medical School, St. Louis, Mo. *Associate Professor of Physiology.* (1, 1927)

Githens, Thomas Stotesbury, M.D. The Cambridge, Wissahickon and Chelten Aves., Germantown, Philadelphia, Pa. (1, 1915)

Givens, Maurice H., Ph.D. 1750 N. Ashland Ave., Chicago, Ill. *Biochemist, Northwestern Yeast Company.* (1, 1917; 2, 1915)

Glaser, O. C., Ph.D. Amherst College, Amherst, Mass. *Professor of Biology.* (1, 1913)

Glazko, Anthony J., Ph.D. 2319 College Ave., Berkeley, Calif. *Naval Laboratory Research Unit No. 1, University of California, Berkeley.* (1, 1942)

Glick, David, Ph.D. Russell-Miller Milling Co. Minneapolis, Minn. *Head, Vitamin and Enzyme Research.* (2, 1936)

Goebel, Walther F., Ph.D. The Rockefeller Institute for Medical Research, 66th St. and York Ave., New York City. *Member.* (2, 1929; 6, 1937)

Goerner, Alfred, Ph.G., Pharm. D., M.D. Long Island College of Medicine, 350 Henry St., Brooklyn, N. Y. *Associate Professor of Biological Chemistry.* (2, 1939)

Goettsch, Marianne, Ph.D. School of Tropical Medicine of Columbia University, San Juan, Puerto Rico. *Assistant Professor of Chemistry.* (2, 1933; 5, 1941)

Gold, Harry, M.D. 1300 York Ave., New York City. *Assistant Professor of Pharmacology, Cornell Medical College.* (3, 1927)

Goldblatt, Harry, M.D. Western Reserve University, Cleveland, O. *Professor of Experimental Pathology, and Associate Director, Institute of Pathology.* (4, 1927)

Goldfarb, Walter, M.D. 120 Station Hospital, A. P. O. 508, New York, N. Y. *Captain, M.C.* (1, 1938)

Goldforb, A. J., Ph.D. College of the City of New York, New York City. *Professor of Biology.* (1, 1930)

Goldie, Horace, M.D., D.T.M. Lederle Laboratories, Pearl River, N. Y. (6, 1943)

Goldring, William, M.D. New York University College of Medicine, 477 First Ave., New York City. *Assistant Professor of Medicine.* (1, 1939)

Goldschmidt, Samuel, Ph.D. University of Pennsylvania Medical School, Philadelphia. *Associate Professor of Physiology.* (1, 1919; 2, 1915)

Goldsmith, Grace A. Tulane University of Louisiana, New Orleans. (5, 1943)

Goodman, Louis Sanford, M.A., M.D. University of Utah School of Medicine, Salt Lake City. *Professor of Pharmacology and Chairman of the Department of Pharmacology and Physiology.* (3, 1937)

Goodner, Kenneth, Ph.D. Rockefeller Institute, 66th St. and York Ave., New York City. *Associate.* (6, 1932)

Goodpasture, Ernest William, M.D. Vanderbilt University Medical School, Nashville, Tenn. *Professor of Pathology,* (4, 1923)

Gordon, Albert S., M.S., Ph.D. Washington Square College of Arts and Sciences, New York University, New York City. *Assistant Professor of Biology.* (1, 1942)

Gordon, Harry H., M.D. 525 E. 68th St., New York City. *Associate in Pediatrics, Cornell University Medical School; Associate Attending Pediatrician, New York Hospital; Medical Officer, U. S. Dept. Labor.* (5, 1940)

Gordon, Irving, M.D. Commission on Acute Respiratory Diseases, Station Hospital #2, Fort Bragg, N. C. (6, 1943)

Gordon, William G., M.A., Ph.D. Eastern Regional Research Laboratory, U. S. Department of Agriculture, Chestnut Hill Station, Philadelphia, Pa. *Chemist.* (2, 1939)

Goss, Harold, Ph.D. University of California College of Agriculture, Davis. *Professor of Animal Husbandry.* (2, 1936; 5, 1933)

Gottschall, Russell Y., M.S., Ph.D. Bureau of Laboratories, Michigan Department of Health, Lansing. *Bacteriologist.* (6, 1939)

Goudsmit, Arnoldus, Jr., M.D., Ph.D. 40 Roberts Avenue, Glenside, Pa. Medical Corps, 232 General Hospital, Camp Barkeley, Texas. (1, 1940)

Govier, William M., M.D. Sharp and Dohme, Inc., Glenolden, Pa. *Pharmacologist—Medical-Research Division.* (3, 1944)

Grabfield, G. Philip, M.D. 27 Forest St., Milton, Mass. *Associate in Medicine and Pharmacology, Harvard Medical School. (At present on leave of absence; Col. M.C., U. S. A.)* (3, 1923)

Grady, Hugh G., M.D. Fitzgerald-Mercy Hospital, Darby, Pa. *Director of Laboratories.* (4, 1940)

Graef, Irving, M.D. New York University College of Medicine, New York City. *Associate Professor of Pathology; Pathologist, Bellevue Hospital and New York University Clinic.* (4, 1941)

Graham, Clarence H., Ph.D. Brown University, Providence, R. I. *Professor of Psychology.* (1, 1933)

Graham, Helen Tredway, A.M., Ph.D. Euclid Ave. and Kingshighway, St. Louis, Mo. *Associate Professor of Pharmacology, Washington University School of Medicine.* (1, 1933; 3, 1931)

Grant, R. Lorimer, M.S., Ph.D. Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington 25, D. C. *Pharmacologist.* (2, 1938)

Graubard, Mark, M.A., Ph.D. 3427 Oakwood Ter., N. W., Washington, D. C. (1, 1940)

Grauer, Robert C., M.D. Allegheny General Hospital, Pittsburgh, Pa. *Head of Department of Research in Endocrinology and Metabolism, William H. Singer Memorial Research Laboratory; Lecturer in Pathology, School of Medicine, University of Pittsburgh.* (4, 1941)

Graves, Stuart, M.D. School of Medicine, University of Alabama, University. *Dean and Professor of Pathology.* (6, 1918)

Gray, John S., M.S., Ph.D. Research Division, School of Aviation Medicine, Randolph Field, Texas. *Assistant Professor of Physiology, Northwestern University Medical School, Chicago, Ill. (on leave).* (1, 1937)

Gray, Samuel H., M.D. The Jewish Hospital of St. Louis, Kingshighway and Forest Park Blvd., St. Louis, Mo. *Pathologist, Jewish Hospital; Director of Laboratories, City Hospitals; Associate Professor of Pathology, Washington University.* (4, 1939)

Greaves, J. D., M.S., Ph.D. 3211 S. W. 10th Ave., Portland, Ore. (2, 1938)

Greaves, Joseph E., Ph.D. Utah State Agricultural College, Logan. *Professor and Head of Department of Bacteriology and Biochemistry.* (2, 1940)

Greeley, Paul O., A.M., Ph.D., M.D. University of Southern California Medical School, University Park, Los Angeles. *Dept. of Aviation Medicine.* (1, 1940)

Green, Arda Alden, M.D. Medical School, Washington University, St. Louis, Mo. *Assistant Professor of Biological Chemistry; Research Associate in Pharmacology.* (2, 1932)

Green, Daniel M., M.S., M.D. Headquarters 73rd Bombardment Wing, APO 17159, c/o Postmaster, San Francisco, Calif. *Instructor, Pharmacology and Therapeutics, University of Tennessee (on leave) Major, 0-291385 M.C.* (3, 1942)

Green, David E., Ph.D. Department of Medicine, College of Physicians and Surgeons, Columbia University, New York City. *Associate in Biochemistry.* (2, 1941)

Green, Harold David, M.D. Western Reserve University, School of Medicine, Cleveland, O. *Associate Professor of Physiology.* (1, 1936)

Green, Robert, M.A., M.D. 223 Millard Hall, University of Minnesota, Minneapolis. *Professor of Bacteriology and Immunology.* (6, 1930)

Greenberg, David Morris, Ph.D. University of California, Berkeley. *Professor of Biochemistry.* (2, 1927)

Greene, Carl Hartley, Ph.D., M.D. 140 E. 54th St., New York City. *Associate Clinical Professor of Medicine, New York Post-Graduate Medical School of Columbia University; Clinical Professor of Medicine, Long Island College of Medicine.* (1, 1921; 2, 1922; 4, 1924)

Greene, Charles Wilson, A.M., Ph.D. 814 Virginia Ave., Columbia, Mo. *Lecturer in Physiology, Stanford University; Professor Emeritus of Physiology and Pharmacology, University of Missouri.* (1, 1900; 2, 1919; 3, 1909)

Greene, Harry S. N., M.D., C.M. Department of Pathology, Yale University School of Medicine, New Haven, Conn. *Professor of Pathology.* (4, 1937)

Greene, James Alexander, M.D. Baylor University College of Medicine, 509 Lincoln St., Houston, Texas. *Professor of Medicine.* (1, 1939)

Greene, James Alexander, M.D. Baylor University, College of Medicine, Buffalo Drive., Houston, Texas. *Professor and Chairman of the Department of Internal Medicine and Dean of the Clinical Faculty.* (1, 1939)

Greene, Ronald R., M.S., M.D. Northwestern University Medical School, 303 E. Chicago Ave., Chicago, Ill. *Instructor in Physiology; Instructor in Obstetrics and Gynecology.* (1, 1941)

Greengard, Harry, Ph.D., M.D. Northwestern University Medical School, 303 E. Chicago Ave., Chicago, Ill. *Assistant Professor of Physiology.* (1, 1939)

Greenstein, Jesse P., Ph.D. National Cancer Institute, Bethesda, Md. *Senior Biochemist.* (2, 1935)

Greenwald, Isidor, Ph.D. 477 First Ave., New York City. *Associate Professor of Chemistry, New York University College of Medicine.* (2, 1912; 5, 1933)

Greep, Roy O., Ph.D. Squibb Institute for Medical Research, New Brunswick, N. J. *Research Associate in Pharmacology.* (1, 1940)

Greer, C. M., M.S. Vanderbilt University School of Medicine, Nashville, Tenn. *Research Associate in Pharmacology.* (3, 1938)

Gregersen, Magnus I., A.M., Ph.D. College of Physicians and Surgeons, Columbia University, 630 W. 168th St., New York City. *Professor of Physiology.* (1, 1933)

Gregg, Donald Eaton, M.S., Ph.D. Department of Medicine, Western Reserve Medical School, 2109 Adelbert Rd., Cleveland, O. *Associate Professor of Physiology.* (1, 1933)

Gresheimer, Esther M., Ph.D., M.D. Temple University Medical School, 3400 N. Broad St., Philadelphia, Pa. *Professor of Physiology.* (1, 1925)

Griffin, Angus, Ph.D. Department of Bacteriology, George Washington University School of Medicine, 1335 H St., N.W., Washington, D. C. *Assistant Professor of Bacteriology.* (6, 1940)

Griffith, Fred R., Jr., M.A., Ph.D. 24 High St., Buffalo, N. Y. *Professor of Physiology, University of Buffalo Medical School.* (1, 1923; 5, 1933)

Griffith, Wendell H., M.S., Ph.D. APO #887, c/o P.M., New York City. *Lt. Col., Office Chief Surgeon, Sanitary Corps, ETOUSA. On leave as Professor of Biochemistry, St. Louis University School of Medicine.* (2, 1923; 5, 1934)

Grimson, Keith S., M.D.* Duke University School of Medicine, Durham, N. C. *Associate Professor of Surgery.* (1, 1943)

Groat, William A., M.D. 713 E. Genesee St., Syracuse, N. Y. *Professor of Clinical Pathology, Syracuse University College of Medicine.* (6, 1917)

Grollman, Arthur, M.D., Ph.D. Southwestern Medical College, 2211 Oak Lawn Ave., Dallas, Texas. *Professor of Experimental Medicine and Lecturer in Physiology and Pharmacology.* (1, 1928; 3, 1933)

Gross, Erwin G., Ph.D., M.D. Medical Laboratories, State University of Iowa, Iowa City. *Professor of Pharmacology.* (1, 1927; 2, 1923; 3, 1927)

Gross, Robert E., M.D. Harvard Medical School, 300 Longwood Ave., Boston, Mass. *Assistant Professor of Surgery.* (4, 1940)

Gruber, Charles M., A.M., M.D., Ph.D. Jefferson Medical College, 1025 Walnut St., Philadelphia, Pa. *Professor of Pharmacology.* (1, 1914; 3, 1919)

Gruhzit, Oswald M., M.D. Research Laboratories, Parke, Davis & Co., Detroit, Mich. *Research in Pathology and Pharmacology.* (4, 1928)

Grundfest, Harry, A.M., Ph.D. 37 Ward Ave., Rumson, N. J. (1, 1932)

Gudernatsch, F., Ph.D. Graduate School, New York University, Washington Square E., New York City. *Visiting Professor.* (1, 1930)

Guerrant, N. B., M.S., Ph.D. Pennsylvania State College, State College. *Professor of Biological Chemistry.* (2, 1934; 5, 1933)

Guest, George Martin, M.S., M.D. The Children's Hospital, Research Foundation, Elland and Bethesda Aves., Cincinnati, O. *Fellow of the Children's Hospital Research Foundation; Associate Professor of Pediatrics, University of Cincinnati, College of Medicine and Graduate School.* (2, 1933)

Gulick, Addison, A.M., Ph.D. 308 Westmount Ave., Columbia, Mo. *Professor of Physiological Chemistry, University of Missouri.* (1, 1915; 5, 1933)

Gunn, Francis D., M.D. University of Utah, School of Medicine, Salt Lake City. *Professor of Pathology.* (4, 1938)

Gurin, S., M.S., Ph.D. University of Pennsylvania School of Medicine, Philadelphia. *Assistant Professor in Physiological Chemistry.* (2, 1938)

Gustavson, Reuben G., Ph.D. University of Colorado, Boulder. *Professor of Chemistry.* (2, 1927)

Gustus, Edwin L., M.Sc., Ph.D. Benning Hall, 3445 38th St., N.W., Washington 16, D. C. *Research and Development Branch, Military Planning Division, OQMG, War Department, Director of Research.* (2, 1934)

Guthrie, Charles Claude, M.D., Ph.D., Sc.D. University of Pittsburgh Medical School, Pittsburgh, Pa. *Professor of Physiology and Pharmacology.* (1, 1905; 3, 1909)

de Gutiérrez-Mahoney, C. G., M.D. 1032 Andalusia Ave., Coral Gables, Fla. *Associate Professor of Neurology, Vanderbilt Univ. School of Medicine, Nashville, Tenn., Lt. Col., M.C., AAF., Regional Station Hospital.* (1, 1940; 4, 1941)

György, Paul, M.D. Babies' and Children's Hospital, Western Reserve University, 2103 Adelbert Rd., Cleveland, O. *Associate Professor of Pediatrics.* (2, 1938; 5, 1939)

Haag, Harvey B., M.D. Medical College of Virginia, Richmond. *Professor of Pharmacology.* (3, 1934)

Haag, J. R., Ph.D. Oregon Agricultural Experiment Station, Corvallis. *Chemist.* (5, 1941)

Hadley, Philip Bardwell, Ph.D. Institute of Pathology, Western Pennsylvania Hospital, Pittsburgh. *Chief of Bacteriological Service and Research Bacteriologist.* (4, 1927)

Hafkesbring, H. Roberta, Ph.D. Woman's Medical College of Pennsylvania, East Falls, Philadelphia. *Associate Professor of Physiology.* (1, 1931)

Haggard, Howard W., M.D. 4 Hillhouse Ave., New Haven, Conn. *Director of the Laboratory*

of Applied Physiology, Yale University. (1, 1919; 2, 1920)

Hahn, Paul F., Ph.D. Vanderbilt University School of Medicine, Nashville, Tenn. *Associate Professor of Biochemistry.* (4, 1939)

Haig, Charles, M.A., Ph.D. New York Medical College, Flower and Fifth Avenue Hospital, Fifth Ave. at 105th St., New York City. *Assistant Professor of Physiology.* (1, 1942)

Haist, Reginald E., M.A., M.D., Ph.D.* University of Toronto, Toronto, Ontario, Canada. *Assistant Professor of Physiology.* (1, 1943)

Haldi, John, A.M., Ph.D. Emory University, Emory University, Ga. (1, 1928)

Hale, Worth, M.D. Harvard Medical School, Boston, Mass. *Associate Professor of Pharmacology.* (1, 1908; 3, 1908)

Hale, Wm. M., M.D. The State University of Iowa College of Medicine, Iowa City. *Professor of Bacteriology.* (4, 1941; 6, 1935)

Hall, F. G., M.A., Ph.D. Duke University, Durham, N. C. *Professor of Zoology.* (1, 1937)

Hall, George Edward, M.D., Ph.D. 1st Floor Annex, Jackson Bldg., Ottawa, Can. *Captain, R.C.A.F.; Associate Professor, Banting Institute, University of Toronto.* (1, 1938)

Hall, Victor E., M.A., M.D. Department of Physiology, Stanford University, Calif. *Professor of Physiology.* (1, 1934)

Halliday, Nellie, Ph.D. Research Laboratory, Mt. Zion Hospital, San Francisco, Calif. (5, 1933)

Halpert, Béla, M.D. University of Oklahoma School of Medicine, Oklahoma City. *Director of Laboratories and Professor of Clinical Pathology.* (4, 1936)

Halsey, John T., M.D. P. O. Box 264, Waveland, Miss. *Professor Emeritus of Pharmacology, Tulane University of Louisiana.* (3, 1929)

Halstead, Ward C., M.A., Ph.D. Dept. of Medicine, University of Chicago, Chicago, Ill. *Associate Professor Experimental Psychology, Division of Psychiatry.* (1, 1942)

Ham, Arthur W., M.B. University of Toronto, Toronto 5, Canada. *Associate Professor of Anatomy, in charge of Histology.* (4, 1939)

Hambourger, Walter E., Ph.D., M.D. G. D. Searle & Co., P. O. Box 5110, Chicago, Ill. *Chief Pharmacologist.* (3, 1934)

Hamilton, Bengt L. K., M.D., ScD. 826 E. 61st St., Chicago, Ill. (2, 1925)

Hamilton, James B., Ph.D. University of Missouri, Dept. of Anatomy, School of Medicine, Columbia. *Associate Professor of Anatomy.* (1, 1938)

Hamilton, Tom S., M.S., Ph.D. 551 Old Agricultural Building, Urbana, Ill. *Professor of Animal Nutrition, University of Illinois.* (2, 1937; 5, 1938)

Hamilton, W. F., Ph.D. University of Georgia School of Medicine, Augusta. *Professor of Physiology and Pharmacology.* (1, 1924)

Hammett, Frederick S., M.S., A.M., Ph.D. 493 Commercial St., Provincetown, Mass. *Scientific Director, Lankenau Hospital Research Institute, Philadelphia, Pa.* (1, 1920; 2, 1917)

Hammon, William McD., M.D., M.P.H., Dr. P.H. 104 Lunado Way, San Francisco, Calif. *Associate Professor of Epidemiology; Lecturer in Tropical Medicine; Lecturer in Nursing.* (4, 1944)

Hampel, C. W., Ph.D. New York University College of Medicine, New York. N. Y. *Visiting Professor of Physiology.* (1, 1936)

Handler, Philip, M.S., Ph.D. Duke University School of Medicine, Durham, N. C. *Assistant Professor of Biochemistry and Nutrition.* (2, 1944)

Handley, Carroll A., Ph.D. Baylor Univ. College of Medicine, Houston 1, Texas. *Professor of Physiology and Pharmacology, and Acting Head of the Department.* (3, 1942)

Haney, Hance F., Ph.D., M.D. University of Oregon Medical School, Portland. *Professor of Physiology and Head of the Department.* (1, 1939)

Hanger, Franklin, M.D. College of Physicians and Surgeons, 630 W. 168th St., New York City. *Associate Professor of Medicine, Columbia University.* (6, 1930)

Hanke, Martin E., Ph.D. University of Chicago, Chicago, Ill. *Associate Professor of Biochemistry.* (2, 1925)

Hanke, Milton Theo., Ph.D. 7550 S. Green St., Chicago, Ill. *Research Consultant, Biochemistry and Nutrition.* (2, 1919)

Hanks, John H., Ph.D. Culion, Palawan, Philippine Islands. (6, 1935)

Hansen, Arild E., M.D. University of Texas Medical School, Galveston. *Professor of Pediatrics and Chairman of the Department; Director of the University of Texas Child Health Program.* (4, 1941; 5, 1942)

Hanzal, Ramon F., M.A., Ph.D. Killian Research Laboratories, 49 W. 45th St., New York City. *Biochemist.* (2, 1935)

Hanzlik, Paul J., A.M., M.D. School of Medicine, Stanford University, Sacramento and Webster Sts., San Francisco, Calif. *Professor of Pharmacology.* (1, 1912; 3, 1912)

Hardy, James Daniel, A.M., Ph.D. Russell Sage Institute of Pathology, 525 E. 68th St., New York City. *Research Associate.* (1, 1939)

Hardy, Mary, D.Sc. The Brearley School, 610 E. 83rd St., New York City. *Teacher of Science.* (1, 1933)

Hare, Kendrick, Ph.D. State University of Iowa, Iowa City. *Assistant Professor of Anatomy.* (1, 1938)

Harger, R. N., M.A., Ph.D. Indiana University School of Medicine, Indianapolis. *Professor of Biochemistry and Toxicology.* (2, 1938)

Harkins, Henry Nelson, M.S., Ph.D., M.D. Johns Hopkins Hospital, Baltimore, Md. *Associate Professor of Surgery, Johns Hopkins University Medical School.* (1, 1942)

Harmon, Paul M., A.M., Ph.D. Indiana University, Bloomington. *Professor of Physiology.* (1, 1930)

Harne, O. G. University of Maryland School of Medicine, Baltimore. *Associate Professor of Histology.* (1, 1935)

Harned, Ben King, M.S., Ph.D. Lederle Laboratories, Pearl River, N. Y. *Research Pharmacologist.* (2, 1931; 3, 1941)

Harris, Albert H., 2nd, M.D. Loudenville, N. Y. (6, 1937)

Harris, Albert Sidney, Ph.D. Western Reserve University School of Medicine, Cleveland, O. *Assistant Professor of Physiology.* (1, 1939)

Harris, Milton, Ph.D. National Bureau of Standards, Washington, D. C. *Director of Research, Textile Foundation Research Associateship.* (2, 1939)

Harris, Robert S. Massachusetts Institute of Technology, Cambridge. *Assistant Professor of Nutritional Biochemistry.* (5, 1941)

Harris, William H., M.D. Tulane University School of Medicine, New Orleans, La. *Assistant Professor of Pathology and Bacteriology.* (4, 1925)

Harrison, Frank, M.S., Ph.D. University of Tennessee College of Medicine, Memphis. *Assistant Professor in Anatomy.* (1, 1941)

Harrison, Ross Granville, M.D., Ph.D., Sc.D. Osborn Zoological Laboratory, New Haven, Conn. *Sterling Professor of Biology, Emeritus, Yale University; Chairman of the National Research Council; Member of the National Academy of Sciences.* (1, 1906)

Harrison, R. Wendell, M.S., Ph.D. Ricketts Laboratory, University of Chicago, Chicago, Ill. *Associate Professor of Bacteriology.* (6, 1934)

Harrop, George A., M.D. The Squibb Institute for Medical Research, New Brunswick, N. J. *Vice-President and Director of Research, E. R. Squibb and Sons.* (2, 1922)

Harrow, Benjamin, M.A., Ph.D. College of the City of New York, Convent Ave. and 139th St., New York City. *Professor of Chemistry.* (2, 1927)

Hart, E. B., B.S. Agricultural College, Madison, Wis. *Professor of Biochemistry, University of Wisconsin.* (2, 1910; 5, 1933)

Hart, E. Ross, M.S., Ph.D. Jefferson Medical College, 1025 Walnut St., Philadelphia, Pa. *Assistant Professor of Pharmacology.* (3, 1944)

Hartley, Geo., Jr., M.A., Ph.D., M.D. Boston University School of Medicine, 80 E. Concord St., Boston, Mass. *Assistant Professor of Pathology.* (4, 1941; 6, 1941)

Hartline, H. K., M.D. Johnson Foundation, University of Philadelphia, Philadelphia, Pa. *Assistant Professor of Biophysics.* (1, 1929)

Hartman, Carl G., A.M., Ph.D. Department of Zoology, University of Illinois, Urbana. *Professor of Zoology and Head of the Department; Member, National Academy of Sciences.* (1, 1921)

Hartman, Frank Alexander, A.M., Ph.D. Department of Physiology, Ohio State University, Columbus. *Professor of Physiology and Chairman of the Department.* (1, 1916)

Hartman, F. W., M.D. Henry Ford Hospital, Detroit, Mich. *Pathologist.* (4, 1927)

Hartmann, Alexis F., M.S., M.D. 500 S. Kingshighway, St. Louis, Mo. *Professor of Pediatrics, Washington University School of Medicine.* (2, 1932)

Harvey, E. Newton, Ph.D. Guyot Hall, Princeton, N. J. *Henry Fairfield Osborn Professor of Biology, Princeton University; Member, National Academy of Sciences.* (1, 1914; 2, 1916)

Hass, George, M.D. Major, M.C. AAF School of Aviation Medicine, Randolph Field, Texas. *Chief, Department of Pathology.* (4, 1939)

Hastings, A. Baird, Ph.D., Sc.D. Harvard Medical School, Boston, Mass. *Hamilton Kuhn Professor of Biological Chemistry; Member, National Academy of Sciences.* (1, 1927, 2, 1921; 5, 1940)

Haterius, Hans O., Ph.D. Wayne University College of Medicine, Detroit, Mich. *Professor of Physiology.* (1, 1936)

Hauck, Hazel M., Ph.D. Cornell University, Ithaca, N. Y. *Professor of Home Economics.* (5, 1941)

Hauge, Siegfred M., Ph.D. Purdue University Agricultural Experiment Station, Lafayette, Ind. *Research Associate in Biochemistry.* (5, 1933)

Haury, Victor G., M.D. 206 Cedar Croft Ave., Audubon, N. J. (3, 1939)

Haven, Frances L., M.A., Ph.D. University of Rochester School of Medicine and Dentistry, 260 Crittenden Blvd., Rochester, N. Y. *Associate in Biochemistry.* (2, 1941)

Hawk, Philip B., M.S., Ph.D. 750 West 50th St., Miami Beach, Fla. *President, Food Research Laboratories, Inc.* (1, 1903; 2, 1906)

Hawkins, J. E., Jr., B.A. (Oxon), Ph.D.* Harvard Medical School, Boston, Mass. *Instructor in Physiology.* (1, 1943)

Hawkins, William Bruce, M.D. University of Rochester School of Medicine and Dentistry, 260 Crittenden Blvd., Rochester, N. Y. *Associate Professor of Pathology.* (4, 1933)

Hawks, Jean E. Division of Home Economics, Michigan State College, East Lansing. *Assoc. Professor of Nutrition.* (5, 1944)

Hawley, Estelle E., Ph.D. Medical School, University of Rochester, Rochester, N. Y. *Research Fellow in Pediatrics.* (5, 1935)

Hayman, J. M., Jr., M.D. Lakeside Hospital, Cleveland, O. *Professor of Clinical Medicine and Therapeutics, Western Reserve University.* (1, 1928; 3, 1932)

Haynes, Florence W., M.A., Ph.D. Harvard Medical School, 25 Shattuck St., Boston, Mass. *Research Fellow in Medicine.* (1, 1937)

Haythorn, Samuel R., M.D. Allegheny General Hospital, 320 E. North Ave., Pittsburgh, Pa. *Director of William H. Singer Memorial Laboratory.* (4, 1925)

Haywood, Charlotte, A.M., Ph.D. Mount Holyoke College, South Hadley, Mass. *Professor of Physiology.* (1, 1939)

Hazen, Elizabeth L., M.A., Ph.D. New York State Department of Health Laboratories, 339 E. 25th St., New York City. *Senior Bacteriologist.* (6, 1931)

Hazleton, Lloyd W., Ph.D. The George Washington University, School of Pharmacy, Washington-D. C. *Assistant Professor of Pharmacology.* (3, 1944)

Heard, R. D. H., M.A., Ph.D. Dalhousie University, Halifax, Nova Scotia. *Assistant Professor of Biochemistry.* (2, 1938)

Hecht, Selig, Ph.D. Columbia University, New York City. *Professor of Biophysics. Member, National Academy of Sciences.* (1, 1920)

Heft, Hattie L., Ph.D. Teachers College, Columbia University, New York City. *Assistant Professor of Physiological Chemistry.* (2, 1927)

Hegnauer, Albert H., Ph.D. Syracuse University, Syracuse, N. Y. *Assistant Professor of Physiology.* (1, 1937)

Hegsted, David Mark, M.S., Ph.D. Schools of Medicine & Public Health, Harvard University, 25 Shattuck St., Boston, Mass. *Associate in Nutrition.* (5, 1944)

Heidelberger, Michael, Ph.D., M.A. 620 W. 168th St., New York City. *Associate Professor of Biological Chemistry, Columbia University; Chemist to the Medical Service, Presbyterian Hospital.* (2, 1927; 6, 1935)

Heilbrunn, Lewis Victor, Ph.D. University of Pennsylvania, Philadelphia. *Professor of Zoology.* (1, 1930)

Heim, J. William, Ph.D. Aero-Medical Laboratory, Army Air Forces, Wright Field, Dayton, O. *Senior Research Physiologist; Assistant in Physiology, Harvard School of Public Health.* (1, 1936)

Heinbecker, Peter, M.D. Washington University Medical School, St. Louis, Mo. *Associate Professor of Surgery.* (1, 1930)

Helff, O. M., M.S., Ph.D. New York University, University Heights, New York City. *Associate Professor of Biology.* (1, 1932)

Hellbaum, Arthur A., M.A., Ph.D. University of Oklahoma School of Medicine, Oklahoma City. *Assistant Professor of Physiology.* (1, 1937)

Hellebrandt, Frances Anna, M.D. Medical College of Virginia, Richmond. *Professor of Physical Medicine.* (1, 1933)

Heller, Victor G., Ph.D. Oklahoma A. & M. College, Stillwater. *Professor and Head of the Department of Agricultural Chemistry Research.* (2, 1935; 5, 1935)

Hellerman, Leslie, Ph.D. Johns Hopkins University School of Medicine, 710 N. Washington St., Baltimore, Md. *Associate in Physiological Chemistry.* (2, 1935)

Helmer, Oscar Marvin, M.S., Ph.D. Lilly Laboratory for Clinical Research, The Indianapolis City Hospital, Indianapolis, Ind. *Head of Department of Physiological Chemistry; Research Associate in the Department of Medicine, Indiana University School of Medicine.* (2, 1935)

Hemingway, Allan, Ph.D. 210 Millard Hall, University of Minnesota, Minneapolis. *Assistant Professor of Physiological Chemistry; Temporarily at School of Aviation Medicine, Randolph Field, Texas.* (1, 1933)

Henderson, Velyien E., M.A., M.B., F.R.S.C. Medical Bldg., University of Toronto, Toronto, Ont., Canada. *Professor of Pharmacology and Pharmacy.* (1, 1905; 3, 1911)

Hendrix, Byron M., Ph.D. School of Medicine, University of Texas, Galveston. *Professor of Biochemistry.* (2, 1920)

Hendrix, James Paisley, M.A., M.D. Duke Hospital, Durham, N. C. *Associate in Medicine (in charge of Therapeutics); Associate in Physiology and Pharmacology, Duke University School of Medicine.* (3, 1942)

Hendry, Jessie L., M.A. Division of Laboratories and Research, New York State Department of Health, New Scotland Ave., Albany. *Senior Bacteriologist.* (6, 1938)

Henle, Werner, M.D. University of Pennsylvania, Philadelphia. *Assistant Professor of Bacteriology in Pediatrics.* (6, 1938)

Henschel, Austin F., Ph.D.* University of Minnesota, Minneapolis. *Physiologist, U. S. War Dept. (QMC), and Instructor in Physiology, University of Minnesota.* (1, 1944)

Hepburn, Joseph Samuel, A.M., M.S., Ph.D., M.D. 235 N. 15th St., Philadelphia 2, Pa. *Professor of Chemistry and Research Associate in Gastro-Enterology, Hahnemann Medical College and Hospital.* (2, 1915)

Hepler, Opal E., Ph.D., M.D. Northwestern University Medical School, 303 E. Chicago Ave., Chicago, Ill. *Assistant Professor of Pathology.* (4, 1939)

Herbst, R. M., Ph.D. 39 Knollwood Road, Short Hills, N. J. *Director of Research, E. Bilhuber, Inc., Orange, N. J.* (2, 1938)

Herrick, C. Judson, Ph.D. 236 Morningside Drive, Grand Rapids, Mich. *Professor Emeritus of Neurology, University of Chicago; Member of the National Academy of Sciences.* (1, 1907)

Herrick, Julia F., M.A., Ph.D. 175 Chelsea Ave., Long Branch, N. J. *Mayo Foundation, Rochester, Minn.* (1, 1933)

Herrin, Raymond C., Ph.D., M.D. University of Wisconsin Medical School, Madison. *Associate Professor of Physiology.* (1, 1932)

Herrington, Lovic P., M.A., Ph.D. 290 Congress Ave., New Haven, Conn. *Associate Director, John B. Pierce Laboratory of Hygiene; Research Associate Professor, Dept. of Public Health, Yale Medical School.* (1, 1942)

Herriott, Roger M., Ph.D. Rockefeller Institute for Medical Research, Princeton, N. J. *Associate.* (2, 1940)

Herrman, George, Ph.D., M.D. University of Texas, Medical Branch, Galveston. *Professor of Medicine.* (4, 1925)

Herrmann, Julian B., M.D. Yale School of Medicine, New Haven, Conn. *Research Assistant in Pharmacology.* (3, 1941)

Herrmann, Louis George, M.D. Cincinnati General Hospital, Cincinnati, O. *Associate Professor of Surgery, University of Cincinnati College of Medicine.* (4, 1933)

Hershey, A. D., Ph.D. Washington University School of Medicine, St. Louis, Mo. *Assistant Professor of Bacteriology and Immunology.* (6, 1942)

Hertig, Arthur T., M.D. Harvard University Medical School, 221 Longwood Ave., Boston, Mass. *Assistant Professor of Pathology and Assistant Professor of Obstetrics.* (4, 1941)

Hertz, Saul, M.D. Massachusetts General Hospital, Fruit St., Boston. *Research Associate, Harvard Medical School and Massachusetts Institute of Technology.* (4, 1935)

Hertzman, Alrick B., Ph.D. St. Louis University School of Medicine, St. Louis, Mo. *Professor of Physiology and Director of the Department.* (1, 1925)

Herwick, Robert P., Ph.D., M.D., LL.B. U. S. Food and Drug Administration, Washington, D. C. *Chief, Drug Division, Associate Prof. Pharmacology, Georgetown Medical School, Adjunct Clinical Professor Medicine (Therapeutics) George Washington Medical School.* (3, 1938)

Hess, Charles L., M.S., M.D. 308 Davidson Bldg., Bay City, Mich. (1, 1916)

Hess, Walter C., Ph.D. Chemo-Medical Research Institute, Georgetown University, Washington, D. C. *Associate Research Professor.* (2, 1935)

Hetherington, Albert W., M.S., Ph.D.* Northwestern University Medical School, 303 E. Chicago Ave., Chicago, Ill. *Instructor in Neurology.* (1, 1943)

Hewitt, Earl Albon, M.S., Ph.D. Iowa State College, Ames. *Associate Professor of Veterinary Physiology.* (1, 1932)

Hewitt, Julia A. W., B.A. Nassau Hospital, Mineola, N. Y. *Senior Technician, in charge.* (6, 1921)

Heyroth, Francis F., M.D., Ph.D. Kettering Laboratory, College of Medicine, University of Cincinnati, Cincinnati, O. *Assistant Professor of Applied Physiology.* (2, 1935)

Hiatt, Edwin P., M.A., Ph.D. North Carolina University School of Medicine, Chapel Hill. *Associate Professor of Physiology and Pharmacology.* (1, 1942)

Hickman, Kenneth C. D., Ph.D. Distillation Products, Inc., 755 Ridge Road W., Rochester, N. Y. *Vice-President and Director of Research.* (2, 1944)

Higgins, Harold Leonard, M.D. 322 Franklin, Newton, Mass. *Assistant Professor of Pediatrics, Harvard University.* (1, 1914; 5, 1933)

Hill, Edgar S., M.S., Ph.D. Washington University, College of Dentistry, St. Louis, Mo. *Associate Professor of Biological Chemistry and Physiology.* (2, 1936)

Hill, Robert M., M.S., Ph.D. 4200 E. 9th Ave., Denver, Colo. *Associate Professor of Biochemistry, University of Colorado Medical School.* (2, 1933)

Hill, Samuel E., M.A., Ph.D. Russell Sage College, Troy, N. Y. *Professor of Biology.* (1, 1934)

Hiller, Alma, Ph.D. Rockefeller Institute for Medical Research, 66th St. and York Ave., New York City. *Associate.* (2, 1929)

Himmelsbach, C. K., M.D. Division of Physiology, U. S. Public Health Service, National Institute of Health, Washington, D. C. *Passed Assistant Surgeon.* (3, 1938)

Himwich, Harold E., M.D. Albany Medical College, Albany, N. Y. *Professor of Physiology and Pharmacology.* (1, 1925; 5, 1933)

Hines, Harry M., M.S., Ph.D. The State University of Iowa, Iowa City. *Professor of Physiology.* (1, 1928)

Hines, Marion, Ph.D. Johns Hopkins Medical School, Baltimore, Md. *Associate Professor of Anatomy.* (1, 1932)

Hinrichs, Marie, Ph.D., M.D. Southern Illinois Normal University, Carbondale. *Associate Professor of Physiology; Head of Student Health Service.* (1, 1928)

Hinsey, Joseph C., M.S., Ph.D. Cornell University Medical College, 1300 York Ave., New York

City. *Professor of Anatomy and Dean of the Medical College.* (1, 1929)

Hisaw, Frederick L., A.M., Ph.D. The Biological Laboratories, Harvard University, Cambridge Mass. *Professor of Zoology.* (1, 1932)

Hitchcock, David I., Ph.D. 333 Cedar St., New Haven, Conn. *Associate Professor of Physiology, Yale University.* (2, 1930)

Hitchcock, Fred A., M.Sc., Ph.D. Ohio State University, Columbus. *Associate Professor of Physiology.* (1, 1927; 5, 1933)

Hitchings, George H., M.S., Ph.D. 17 Priscilla Ave., Tuckahoe, N. Y. *Biochemist, Burroughs, Wellcome & Co.* (2, 1942)

Hjort, Axel M., M.D., Ph.D. P. O. Box 281, 14 Fern Way, Scarsdale, N. Y. *Adjunct Physician, Grasslands Hospital, Valhalla, N. Y.* (2, 1925)

Hoagland, Charles L., M.D. Rockefeller Institute, 66th St. and York Ave., New York City. *Associate Member.* (6, 1940)

Hoagland, Hudson, M.S., Ph.D. Worcester State Hospital, Worcester, Mass. (1, 1932)

Höber, Rudolf. University of Pennsylvania Medical School, Philadelphia. *Visiting Professor of Physiology.* (1, 1936)

Hodes, Robert, Ph.D. Johnson Foundation, University of Pennsylvania, Philadelphia. *Johnson Foundation Fellow in Medical Physics.* (1, 1941)

Hodge, Harold C., Ph.D. University of Rochester School of Medicine and Dentistry, Rochester, N. Y. *Associate Professor of Biochemistry and Pharmacology.* (2, 1937)

Hoff, Ebbe Curtis, M.A., Ph.D. Department of Physiology, Yale University School of Medicine, 333 Cedar St., New Haven, Conn. (1, 1933)

Hoff, Hebbel E., M.A., Ph.D. McGill University, Montreal, Quebec, Canada. *Professor of Physiology.* (1, 1933)

Hoffman, Olive, M.S., Ph.D. Presbyterian Hospital, 51 N. 39th St., Philadelphia, Pa. (1, 1935)

Hoffman, William Samuel, Ph.D., M.D. 629 S. Wood St., Chicago, Ill. *Acting Director of Laboratories and Acting Director of the Hektoen Institute for Medical Research, Cook County Hospital.* (2, 1935)

Hogan, Albert G., A.M., Ph.D. 105 Schweitzer Hall, Columbia, Mo. *Professor of Animal Nutrition, University of Missouri.* (2, 1916; 5, 1933)

Hogness, Thorfin R., Ch.E., Ph.D. Department of Chemistry, University of Chicago, Chicago, Ill. *Professor of Chemistry.* (2, 1941)

Holck, Harald G. O., Ph.D. College of Pharmacy, University of Nebraska, Lincoln. *Associate Professor of Pharmacology.* (1, 1935; 3, 1938)

Hollander, Franklin, Ph.D. Mount Sinai Hospital, Fifth Ave. and 100th St., New York City. *Associate in Physiology; Head, Gastro-Enterology Research Laboratory.* (1, 1942; 2, 1932)

Holman, Russell Lowell, M.D. University of North Carolina School of Medicine, Chapel Hill. *Professor of Pathology.* (4, 1940)

Holmes, Arthur Dunham, Ph.D. Massachusetts State College, Amherst. *Research Professor of Chemistry.* (2, 1931; 5, 1933)

Holmes, Julia O., M.S., Ph.D. Massachusetts State College, Amherst. *Research Professor of Nutrition.* (2, 1942; 5, 1936)

Holt, Joseph Paynter, M.S., M.D., Ph.D. University of Louisville School of Medicine, 101 W. Chestnut St., Louisville, Ky. *Associate Professor of Physiology.* (1, 1942)

Holt, L. Emmett, Jr., M.D. 477 First Ave., New York 16, N. Y. (2, 1930)

Hoobler, Icie Macy, Ph.D. 660 Frederick St., Detroit, Mich. *Director of Research, Children's Fund of Michigan; Associate in Nutrition, Medical Staff of the Children's Hospital of Michigan.* (2, 1925; 5, 1933)

Hooker, Davenport, M.A., Ph.D. University of Pittsburgh School of Medicine, Pittsburgh, Pa. *Professor of Anatomy.* (1, 1920)

Hooker, Donald R., M.S., M.D. 19 W. Chase St., Baltimore, Md. *Lecturer in Physiological Hygiene, School of Hygiene and Public Health, Johns Hopkins University; Managing Editor of American Journal of Physiology, Physiological Reviews and Federation Proceedings.* (1, 1906; 3, 1911)

Hooker, Sanford B., A.M., M.D. 80 E. Concord St., Boston, Mass. *Member, Evans Memorial.* (6, 1918)

Hoppert, C. A., Ph.D. Michigan State College, Box 626, East Lansing. *Professor of Biological Chemistry.* (5, 1935)

Horsfall, Frank L., Jr., M.D., C.M. Rockefeller Institute, 66th St. and York Ave., New York City. *Member.* (6, 1937)

Horvath, Steven M., M.A., Ph.D.* Armored Forces Medical Research Laboratory, Ft. Knox, Ky. *Captain, San. Corps.* (1, 1943)

Horwitt, M. K., Ph.D. Biochemical Research Laboratory, Elgin State Hospital, Elgin, Ill. *Director, Biochemical Research Laboratory; Assistant Professor, Physiological Chemistry, University of Illinois School of Medicine.* (2, 1941)

Hoskins, R. G., Ph.D., M.D. Harvard Medical School, Boston, Mass. *Research Associate in Physiology, Harvard University; Director of Research, Memorial Foundation for Neuroendocrine Research.* (1, 1911)

Hotchkiss, Rollin D., Ph.D. The Rockefeller Institute for Medical Research, 66th St. and York Ave., New York City. *Lieut. Commander, Hospital Corps, USNR.* (2, 1941)

Howard, Evelyn, A.M., Ph.D. Johns Hopkins School of Medicine, Baltimore, Md. *Instructor in Physiology.* (1, 1933)

Howard, Marion E., M.D. New Haven Hospital, New Haven, Conn. *Assistant Professor of Medicine, Yale School of Medicine; Associate Physician, New Haven Hospital and New Haven Dispensary.* (4, 1939; 6, 1937)

Howe, Paul E., A.M., Ph.D. 2823 29th St. N.W., Washington, D. C. *Colonel, Sanitary Corps; Chief, Nutrition Branch, Office of the Surgeon General, U. S. Army. On leave as Chief, Animal Nutrition Division, and Assistant Chief, Bureau of Animal Industry, U. S. Department of Agriculture.* (1, 1913; 2, 1909; 5, 1933)

Howe, Percy R., M.D., D.D.S. Harvard Medical School, Boston, Mass. *Director Forsyth Dental Infirmary; Professor Dental Sciences; Instructor in Pathology.* (5, 1935)

Howell, Katherine M., M.D. Michael Reese Hospital, 2900 Ellis Ave., Chicago, Ill. *Head of Departments of Bacteriology and Serology.* (6, 1940)

Howell, Stacey F., Ph.D. V. D. Research Laboratory, U. S. Marine Hospital, Stapleton, Staten Island, N. Y. *Chemist, U. S. Public Health Service.* (2, 1940)

Howell, William H., Ph.D., M.D., Sc.D., LL.D. 112 St. Dunstan's Road, Baltimore, Md. *Professor Emeritus of Physiology, Johns Hopkins University; Member, National Academy of Sciences.* (1, 1887; 2, 1912)

Hubbard, Roger Sanford, A.M., Ph.D. 100 High St., Buffalo, N. Y. *Biochemist, Buffalo General Hospital; Professor of Applied Physiology, Buffalo University Medical School.* (1, 1922; 2, 1920)

Hubbell, Rebecca B., M.S., Ph.D. Connecticut Agricultural Experiment Station, New Haven. *Assistant Biochemist.* (2, 1937; 5, 1935)

Hudack, Stephen Sylvester, M.D. U. S. Naval Hospital, Brooklyn, N. Y. *Lt. Com.* (4, 1933)

Huddleston, Ora Leonard, M.D., Ph.D. Fitzsimmons General Hospital, Denver, Colo. *Major, MC; Instructor in Physiology, University of Colorado School of Medicine.* (1, 1936)

Hueper, Wilhelm C., M.D. Warner Institute for Therapeutic Research, 113 W. 18th St., New York City. *Assistant Director and Principal Pathologist.* (4, 1940)

Huffman, C. F., M.S., Ph.D. Michigan State College, East Lansing. *Research Professor and Associate Professor in Dairy Husbandry.* (5, 1937)

Huggins, Charles Brenton, M.D. University of Chicago, Chicago, Ill. *Professor of Surgery.* (1, 1932)

Hughes, Joseph, M.D. 111 N. 49th St., Philadelphia, Pa. *Assistant Professor of Experimental Neurology, Graduate School of Medicine, University of Pennsylvania; Director of Laboratory, Pennsylvania Hospital for Mental Diseases.* (1, 1936)

Hughes, Josiah Simpson, M.A., M.S., Ph.D. Kansas State College, Manhattan. *Professor of Chemistry.* (2, 1931; 5, 1939)

Hughes, Thomas P., A.M., Ph.D. Rockefeller Foundation, 49 W. 49th St., New York City. *Member of Staff, International Health Division.* (6, 1934)

Hulpieu, Harold R., M.A., Ph.D. Indiana University School of Medicine, Indianapolis. *Associate Professor of Pharmacology.* (3, 1939)

Hunscher, Helen A., Ph.D. Western Reserve University, 2023 Adelbert Rd., Cleveland, O. *Head of Department of Home Economics.* (5, 1934)

Hunt, Reid, M.D., Ph.D., Sc.D. Harvard Medical School, Boston, Mass. *Professor Emeritus of Pharmacology, Harvard University; Member, National Academy of Sciences.* (1, 1895; 2, 1906; 3, 1908)

Hunter, Andrew, M.A., M.B., F.R.S.C. University of Toronto, Toronto, Canada. *Professor of Pathological Chemistry.* (2, 1908)

Hunter, George, M.A., D.Sc., F.R.S.C. University of Alberta, Edmonton, Canada. *Professor of Biochemistry.* (2, 1924)

Hunter, Jesse E., M.S., Ph.D. Allied Mills, Inc., 7500 S. Adams St., Peoria, Ill. *Director Biological Research.* (5, 1936)

Hussey, Raymond, M.D. Homewood Apartments, Baltimore, Md. (4, 1927)

Ingalls, Mabel S., Ph.D. 1218 Bank St., N. W., Washington 7, D. C. (6, 1940)

Ingle, Dwight J., M.S., Ph.D. The Upjohn Co., Research Department, Kalamazoo, Mich. *Upjohn Research Fellow.* (1, 1939)

Ingraham, Raymond Clifford, Ph.D. College of Medicine, University of Illinois, 1853 W. Polk St., Chicago. *Assistant Professor in Physiology.* (1, 1938)

Ingram, W. R., Ph.D. College of Medicine, The State University of Iowa, Iowa City. *Professor and Head of the Department of Anatomy.* (1, 1936)

Irvin, J. Logan, Ph.D. Johns Hopkins University School of Medicine, 710 N. Washington St., Baltimore, Md. *Associate in Physiological Chemistry.* (2, 1942)

Irving, Laurence, A.M., Ph.D. Swarthmore College, Swarthmore, Pa. *Professor of Experimental Biology.* (1, 1927)

Irwin, Marian, Ph.D. The Rockefeller Institute for Medical Research, New York City. *Associate in the Division of General Physiology.* (1, 1927)

Irwin, M. R., Ph.D. Department of Genetics, University of Wisconsin, Madison. *Professor of Genetics.* (6, 1936)

Isaacs, Raphael, M.D. 104 S. Michigan Ave., Suite 630, Chicago 3, Ill. *Director, Department of Hematology, Michael Reese Hospital.* (4, 1928)

Isenberger, R. M., M.A., M.D. University of Kansas School of Medicine, Kansas City. *Professor of Pharmacology.* (3, 1937)

Ivy, Andrew C., Ph.D., M.D. 303 E. Chicago Ave., Chicago, Ill. *Nathan Smith Davis Professor of Physiology and Professor of Pharmacology, Northwestern University Medical School.* (1, 1919; 5, 1933)

Izquierdo, J. Joaquin, M.D. National School of Medicine, Mexico City. *Professor of Physiology in the National School of Medicine and the Escuela Medico Militar of Mexico.* (1, 1928)

Jackson, Dennis Emerson, A.M., Ph.D., M.D. University of Cincinnati Medical School, Eden and Bethesda Aves., Cincinnati, O. *Professor of Pharmacology.* (1, 1910; 3, 1912)

Jackson, Eugene L., Ph.D. Emory University, Ga. *Associate Professor of Pharmacology, Chairman, Department of Pharmacology.* (3, 1942)

Jackson, Richard W., Ph.D. Eastern Regional Research Laboratory, U. S. Department of Agriculture, Wyndmoor, Pa. *Chief of Protein Division.* (2, 1930; 5, 1933)

Jacobs, Merkel Henry, Ph.D. University of Pennsylvania, Philadelphia. *Professor of General Physiology; Member of the National Academy of Sciences.* (1, 1919)

Jacobs, Walter A., A.M., Ph.D. Rockefeller Institute, 66th St. and York Ave., New York City. *Member; Member, National Academy of Sciences.* (2, 1908; 3, 1913)

Jacobson, Edmund, Ph.D., M.D. Laboratory for Clinical Physiology, 310 S. Michigan Ave., Chicago, Ill. (1, 1929)

Jaffe, Henry L., M.D. Hospital for Joint Diseases, 1919 Madison Ave., New York City. *Director of Laboratories.* (4, 1925)

Jahn, Theodore Louis, Ph.D.* State University of Iowa, Iowa City. *Associate Professor of Zoology.* (1, 1944)

Jamieson, Walter A., Sc.D.(hon.). Eli Lilly & Company, Indianapolis, Ind. *Director, Biological Division.* (6, 1927)

Jaques, L. B., M.A., Ph.D.* University of Toronto, Toronto 5, Canada. *Assistant Professor, Dept. of Physiology.* (1, 1943)

Jasper, Herbert H., M.A., Ph.D., D. ès Sci. Montreal Neurological Institute, 3801 University St., Montreal, Que., Canada. *Lecturer in Neuroelectrography and Director of Department of Electrophysiology.* (1, 1940)

Jeans, P. C., M.D. State University of Iowa, Iowa City. *Professor of Pediatrics.* (5, 1937)

Jensen, H., Ph.D. Des Bergers-Bismol Labs. 338 St. Paul St., W. Montreal, Que., Canada. *Director of Research.* (2, 1929)

Jobling, James W., M.D. Columbia University, 630 W. 168th St., New York City. *Professor of Pathology.* (4, 1913)

Jochim, Kenneth E., Ph.D. Michael Reese Hospital, 29th and Ellis Ave., Chicago, Ill. *Research Associate, Cardiovascular Dept.* (1, 1942)

Johlin, J. M., Ph.D., D.Sc. Vanderbilt University School of Medicine, Nashville, Tenn. *Associate Professor of Biochemistry.* (2, 1928)

Johnson, Charles C., M.D. 208 South 8th East, Apt. 9, Salt Lake City, Utah. (3, 1929)

Johnson, Frank H., A.M., Ph.D. Princeton University, Princeton, N. J. *Assistant Professor, Dept. of Biology.* (1, 1942)

Johnson, Joseph L., Ph.D., M.D. School of Medicine, Howard University, Washington, D. C. *Professor and Head of the Department of Physiology.* (1, 1934)

Johnson, J. Raymond, Ph.D. Long Island College of Medicine, 350 Henry St., Brooklyn, N. Y. *Assistant Professor of Physiology and Pharmacology.* (1, 1938)

Johnson, Marvin J., M.S., Ph.D. University of Wisconsin, Madison. *Associate Professor of Biochemistry.* (2, 1941)

Johnson, Robert E., M.D., D. Phil.* Harvard Fatigue Laboratory, Morgan Hall, Soldiers Field, Boston, Mass. *Assistant Professor, Industrial Physiology.* (1, 1944; 2, 1939)

Johnson, Treat B., Ph.D. Amity Road, Bethany, Westville P. O., Conn. *Sterling Professor of Chemistry, Yale University; Member, National Academy of Sciences.* (2, 1910)

Johnson, Victor, Ph.D., M.D. 5807 Dorchester Ave., Chicago, Ill. *Associate Professor of Physiology; Dean of Students in the Division of Biology and the School of Medicine, University of Chicago.* (1, 1933)

Johnston, Charles G., M.S., M.D. Wayne University College of Medicine, Detroit, Mich. *Professor of Surgery.* (1, 1933)

Johnston, Margaret W., Ph.D. Box 276, Ann Arbor, Mich. *Research Associate in Internal Medicine.* (2, 1930; 5, 1938)

Jolliffe, Norman, M.D. 39 E. 75th St., New York, N. Y. (1, 1932)

Jones, D. Breese, Ph.D. Bureau of Human Nutrition and Home Economics, Agricultural Research Administration, U. S. Department of Agriculture, Washington, D. C. *Protein Chemist.* (2, 1920; 5, 1935)

Jones, James H., M.S., Ph.D. School of Medicine, University of Pennsylvania, Philadelphia. *Associate Professor of Physiological Chemistry.* (2, 1928; 5, 1933)

Jones, Kenneth K., M.S., Ph.D. Northwestern University Medical School, 303 E. Chicago Ave., Chicago, Ill. *Associate Professor of Physiology and Pharmacology.* (1, 1936)

Jones, Lloyd R., M.S., Ph.D. 1402 S. Grand Blvd., St. Louis, Mo. *Associate Professor and Chairman of Department of Bacteriology, St. Louis University School of Medicine.* (6, 1933)

Joslin, Elliott P., M.A., M.D. New England Deaconess Hospital, 81 Bay State Rd., Boston, Mass. *Director, George F. Baker Clinic.* (5, 1933)

Jukes, Thomas Hughes, Ph.D. Lederle Laboratories, Pearl River, N. Y. *Associate Director, Pharmaceutical Division.* (2, 1935; 5, 1938)

Jung, Frederic Theodore, Ph.D., M.D. Northwestern University Medical School, Chicago, Ill. *Assistant Professor of Physiology and Pharmacology.* (1, 1930)

Jungeblut, Claus W., M.D. College of Physicians and Surgeons, 630 W. 168th St., New York City. *Professor of Bacteriology, Columbia University.* (4, 1929; 6, 1926)

Kabat, Elvin A., A.M., Ph.D. The Neurological Institute, 710 W. 168th St., New York City. *Research Chemist.* (2, 1940; 6, 1943)

Kabat, Herman, Ph.D., M.D. National Institute of Health, Bethesda, Md. *Pharmacologist.* (1, 1941)

Kahn, Reuben L., Sc.D., LL.D. University of Michigan Hospital, Ann Arbor. *Director of Clinical Laboratories.* (4, 1934; 6, 1919)

Kalckar, Herman M., M.D., Ph.D. Department of Nutrition and Physiology, Public Health Research Institute of the City of New York, Foot of East 15th St., New York City. *Research Associate.* (2, 1942)

Kamm, Oliver, M.S., Ph.D. Research Laboratory, Parke, Davis & Co., Detroit, Mich. *Scientific Director.* (2, 1928)

Karpovich, Peter V., M.D., M.P.E. School of Aviation Medicine, Randolph Field, Texas. *Senior Physiologist, Research Section.* (1, 1942)

Karr, Walter G., Ph.D. Smith, Kline & French Laboratories, Delaware Ave. & Poplar St., Philadelphia 23, Pa. *Director of the Research Laboratories; Assistant Professor of Physiological Chemistry, University of Pennsylvania; Consulting Biochemist to the Medical Clinic of the University Hospital, Bryn Mawr Hospital, Abington Memorial Hospital.* (2, 1925)

Karshan, Maxwell, Ph.D. Department of Biological Chemistry, Columbia University, 630 W. 168th St., New York City. *Associate Professor of Biochemistry.* (2, 1939)

Karsner, Howard T., M.D. Western Reserve University, 2085 Adelbert Rd., Cleveland, O. *Professor of Pathology; Director of the Institute of Pathology.* (4, 1913; 6, 1925)

Katz, Gerhard, M.D. Tulane School of Medicine, New Orleans, La. *Assistant Professor of Pharmacology.* (3, 1937)

Katz, Louis Nelson, A.M., M.D. 2900 Ellis Ave., Chicago, Ill. *Director of Cardiovascular Research, Michael Reese Hospital; Professorial Lecturer in Physiology, University of Chicago.* (1, 1924)

Katzman, Philip A., Ph.D. St. Louis University School of Medicine, 1402 S. Grand Blvd., St. Louis 4, Mo. *Assistant Professor of Biochemistry.* (2, 1935)

Kaulbersz, Jerzy, Ph.D., M.D.* Wayne University College of Medicine, 1512 St. Antoine St., Detroit, Mich. *Research Associate in Surgery and Research Physiology.* (1, 1944)

Kay, H. D., Ph.D., D.Sc. National Institute for Research in Dairying, Shinfield, near Reading, England. *Director, Research Professor of Biochemistry, University of Reading.* (2, 1930)

Keeton, Robert W., M.S., M.D. University of Illinois College of Medicine, 1853 W. Polk St., Chicago. *Professor of Medicine.* (1, 1916; 3, 1924)

Kehoe, Robert A., M.D. Kettering Laboratory of Applied Physiology, College of Medicine, University of Cincinnati, Eden Ave., Cincinnati, O. *Research Professor of Physiology.* (1, 1940)

Keith, Norman M., M.D. Mayo Clinic, Rochester, Minn. *Consulting Physician, Division of Medicine, Mayo Clinic; Professor of Medicine, Mayo Foundation, University of Minnesota.* (1, 1920; 3, 1932; 4, 1924)

Keith, T. B., Ph.D. Pennsylvania State College, State College. *Assistant Professor of Animal Husbandry.* (5, 1941)

Keller, Allen D., Ph.D. Baylor College of Medicine, Houston, Texas. *Professor of Physiology; Chairman of Department of Physiology and Pharmacology.* (1, 1931)

Kelser, Raymond A., Ph.D. 17 Oxford St., Chevy Chase, 15, Md. *Brig. General, U. S. Army.* (4, 1932)

Kelsey, F. Ellis, Ph.D. University of Chicago, Chicago, Ill. *Research Associate (Instructor) in Pharmacology.* (3, 1941)

Kelsey, Frances Kathleen O., M.S., Ph.D. University of Chicago, Chicago, Ill. *Research Assistant in Pharmacology.* (3, 1941)

Kempner, Walter, M.D. Duke University School of Medicine, Durham, N. C. *Assistant Professor of Medicine.* (1, 1940)

Kendall, Edward C., M.S., Ph.D., D.Sc. 62 Eighth Ave., S.W., Rochester, Minn. *Professor of Biochemistry, Mayo Foundation, University of Minnesota.* (1, 1916; 2, 1913; 4, prior to 1920)

Kendall, Forrest E., Ph.D. 240-06—53rd Ave. Douglaston, Long Island, N. Y. *Assistant Professor of Biochemistry, Research Service, Co-*

lumbia Division, Goldwater Memorial Hospital, Welfare Island, N. Y. (6, 1943)

Kennard, Margaret A., M.D. Psychiatric Division, Bellevue Hospital, First Ave. & 30th St., New York City. (1, 1934)

Kennedy, Cornelia, M.A., Ph.D. Snyder Hall, University Farm, St. Paul, Minn. *Associate Professor of Agricultural Biochemistry, University of Minnesota; Assistant Chemist, Minnesota Experiment Station.* (2, 1924; 5, 1934)

Kennedy, Robert P., M.D. Knollwood Drive, R. D. 1, Rochester, N. Y. (4, 1929)

Kenton, Harold B., Ph.D. New England Deaconess Hospital, Boston, Mass. *Bacteriologist and Director of the Blood Bank.* (6, 1934)

Kenyon, Allan T., M.D. University of Chicago, Division of Biological Sciences, 950 E. 59th St., Chicago, Ill. *Assistant Professor of Medicine.* 3, 1940)

Keresztesy, John C., M.A., Ph.D. Merck & Company, Inc., Rahway, N. J. *Head, Nutritional Research Laboratory.* (2, 1941)

Kerr, Stanley E., Ph.D. Near East College Association, 50 W. 50th St., New York City. *Professor of Biological Chemistry, American University of Beirut, Beirut, Syria, Republic of Lebanon.* (2, 1937)

Kerr, Wm. J., M.D. University of California Hospital, Third and Parnassus Aves., San Francisco. *Professor of Medicine, University of California; Physician-in-Chief, University of California Hospital.* (3, 1930)

Kesten, Homer D., M.D. College of Physicians and Surgeons, Columbia University, New York City. *Associate Professor of Pathology.* (4, 1931)

Keys, Ancel, M.A., Ph.D., D. Phil. Stadium South Tower, University of Minnesota, Minneapolis. *Professor of Physical Education and Physiology.* (1, 1939; 2, 1936)

Khorazo, Devorah, M.D. Apt. 4G, 480 W. 187th St., New York City. *Instructor in Bacteriology, Columbia University, Eye Institute.* (6, 1936)

Kidd, John G., M.D. Cornell University Medical College, 1300 York Ave., New York City. *Professor of Pathology; Pathologist, New York Hospital.* (4, 1938; 6, 1937)

Kik, M. C., Ph.D. College of Agriculture, University of Arkansas, Fayetteville. *Assistant Professor of Agricultural Chemistry.* (5, 1942)

Kilborn, Leslie G., M.A., M.D., Ph.D. 250 Golfdale Road, Toronto, Ontario, Canada. (1, 1928)

Killian, John Allen, A.M., Ph.D. Killian Research Laboratories, Inc., 49 W. 45th St., New York City. (2, 1921)

King, Barry G., M.A., Ph.D. College of Physicians and Surgeons, Columbia University, 630 West 168th St., New York City. *Assistant Professor of Physiology; Lieutenant, USNR, Naval Medical Research Institute, Bethesda, Md.* (1, 1938)

King, Charles Edwin, Ph.D. Vanderbilt University, Nashville, Tenn. *Associate Professor of Physiology.* (1, 1916)

King, Charles Glen, Ph.D. Nutrition Foundation, Inc., Chrysler Building, New York City. *Scientific Director.* (2, 1931; 5, 1933)

King, Jessie Luella, Ph.D. Goucher College, Baltimore, Md. *Professor of Physiology.* (1, 1914)

King, Joseph T., M.D., Ph.D. 314 Millard Hall, University of Minnesota Medical School, Minneapolis. *Assistant Professor of Physiology.* (1, 1931)

King, Lester, S., M.D. The Fairfield State Hospital, Newtown, Conn. *Hospital Pathologist.* (4, 1941)

Kinsman, Gladys M., M.A., Ph.D. University of Illinois, Urbana. *Prof. of Nutrition, Dept of Home Ec.; Chief in Nutrition, Agr. Exper. Sta.* (5, 1944)

Kirk, Paul L., Ph.D. University of California, Berkeley. *Associate Professor of Biochemistry.* (2, 1933)

Kirkbride, Mary B., Sc.D. Division of Laboratories and Research, New York State Department of Health, Albany. *Associate Director.* (6, 1921)

Kisch, Bruno, M.D.* 845 West End Ave., New York City. *Professor at Yeshiva College; In Charge of Experimental Medicine at Beth Israel Hospital.* (1, 1943)

Kleiber, M., D.Sc.* University of California, Davis. *Professor of Animal Husbandry.* (1, 1943; 5, 1933)

Klein, J. Raymond, Ph.D. University of Illinois, Neuropsychiatric Institute, 912 S. Wood St., Chicago. *Biochemist and Assistant Professor of Psychiatry and Physiological Chemistry.* (2, 1941)

Kleiner, Israel Simon, Ph.D. New York Medical College, Flower and Fifth Avenue Hospitals, New York 29, N. Y. *Professor of Physiology and Biochemistry.* (1, 1911; 2, 1912; 3, 1912; 5, 1933)

Kleitman, Nathaniel, A.M., Ph.D. University of Chicago, Chicago, Ill. *Associate Professor of Physiology.* (1, 1923)

Klemperer, Friedrich Wilhelm, M.D., Massachusetts General Hospital, Boston, Mass. *Assistant in Medicine.* (2, 1941)

Kletzien, Seymour W., M.S., Ph.D., 22 Lafayette Blvd., Williamsville, N. Y. *Biochemist.* (5, 1933)

Kline, O. L., Ph.D. U. S. Department of Agriculture, Food and Drug Administration, Washington, D. C. *Biochemist.* (5, 1936)

Klüver, Heinrich, Ph.D. University of Chicago, Chicago, Ill. *Member, Otho S. A. Sprague Memorial Institute.* (1, 1935)

Knoefel, Peter K., M.A., M.D. University of Louisville, 101 W. Chestnut St., Louisville, Ky. *Professor of Pharmacology.* (3, 1934)

Knowlton, Frank P., A.M., M.D. Syracuse University College of Medicine, Syracuse, N. Y. *Professor of Physiology.* (1, 1911)

Knowlton, G. Clinton, Ph.D. University of Iowa, Iowa City. *Assistant Professor of Physiology.* (1, 1938)

Knudson, Arthur, Ph.D. Albany Medical College, New Scotland Ave., Albany, N. Y. *Professor of Biochemistry and Associate Dean.* (2, 1919; 5, 1936)

Knutti, Ralph Eddy, M.D. University of Rochester School of Medicine and Dentistry, 260 Crittenden Blvd., Rochester, N. Y. *Assistant Professor of Pathology.* (4, 1933)

Kober, Philip A., B.S. Sherman Laboratories, Detroit, Mich. *Director of Research.* (2, 1912)

Koch, Elizabeth M., M.A., Ph.D. 1534 E. 59th St., Chicago, Ill. (2, 1925)

Koch, Fred Conrad, M.S., Ph.D. 1534 East 59th St., Chicago, Ill. *Director of Biochemical Research, Armour and Co.; Professor of Biochemistry Emeritus, University of Chicago.* (2, 1912; 5, 1933)

Kochakian, Charles D., A.M., Ph.D. University of Rochester Medical School, 260 Crittenden Blvd., Rochester, N. Y. *Assistant Professor, Dept. of Vital Economics.* (1, 1942)

Kocher, Rudolph Alfred, M.D. Box 926, Carmel, Calif. *Director, Velie Metabolic Clinic.* (2, 1915)

Koehler, Alfred E., M.D., Ph.D. 317 W. Pueblo St., Santa Barbara, Calif. *Physician, Sansum Clinic, Santa Barbara Cottage Hospital.* (2, 1924)

Koehne, Martha, Ph.D. Ohio State Department of Health, 75 Eighteenth Ave., Columbus. *Nutritionist.* (5, 1933)

Koepf, George F., M.D. Buffalo General Hospital, 100 High St., Buffalo, N. Y. *Instructor in Medicine, University of Buffalo.* (1, 1942)

Koerber, Walter L., Ph.D. E. R. Squibb & Sons, New Brunswick, N. J. *Assistant Department Head.* (6, 1943)

Kohn, Henry I., Ph.D. 645 Vanderbilt Hall, Longwood Ave., Boston 15, Mass. *Assistant Professor of Physiology and Pharmacology.* (1, 1940)

Kolmer, John A., M.S., M.D., D.P.H., Sc.D., LL.D., L.H.D. 1 Montgomery Ave., Bala-Cynwyd, Pa. *Professor of Medicine, Temple University; Director, Research Institute of Cutaneous Medicine.* (6, 1913)

Komarov, Simon A., M.S., M.D., Ph.D. S. S. Fels Fund, Med. Research Laboratory, 255 S. 17th St., Philadelphia, Pa. *Director of Dept. of Biochemistry.* (1, 1933)

Kopeloff, Nicholas, Ph.D. New York State Psychiatric Institute, 722 W. 168th St., New York City. *Principal Research Bacteriologist, New York State Psychiatric Institute and Hospital.* (6, 1937)

Koppanyi, Theodore, Ph.D. Georgetown University, Washington, D. C. *Professor of Pharmacology.* (1, 1924; 3, 1935)

Korr, Irwin M., M.A., Ph.D. 175 Pinckney Rd., Red Bank, N. J. *Physiologist, U. S. Signal Corps, Ft. Monmouth Signal Laboratories.* (1, 1939)

Kozelka, Frank L., Ph.D. Dept. of Pharmacology and Toxicology, University of Wisconsin, Madison. *Assistant Professor of Toxicology. On leave. Captain, Sn.C.* (3, 1939)

Krahl, Maurice E., Ph.D. Dept. of Pharmacology, College of Physicians and Surgeons, 630 W. 168th St., New York City. (2, 1939)

Kramer, Benjamin, A.M., M.D. 6 Pierrepont St., Brooklyn, N. Y. *Pediatrician-in-Chief, Brooklyn Jewish Hospital; Professor of Clinical Pediatrics, Long Island College Medical School.* (1, 1915; 2, 1914)

Kramer, Martha, Ph.D. Department of Home Economics, Yenching University, Peiping, China. *Professor of Food Economics and Nutrition.* (5, 1933)

Krantz, John C., Jr., M.S., Ph.D. University of Maryland Medical School, Baltimore. *Professor of Pharmacology.* (3, 1937)

Krauss, William E., Ph.D. Ohio Experiment Station, Wooster. *Chief, Dairy Department.* (2, 1932; 5, 1933)

Kraybill, Henry R., M.S., Ph.D. 5720 Woodlawn Ave., Chicago 37, Ill. *Professorial Lecturer, Department of Biochemistry, University of Chicago; Director, Department of Scientific Research, American Meat Institute.* (2, 1942)

Krayer, Otto, M.D. Harvard Medical School, 25 Shattuck St., Boston, Mass. *Associate Professor of Comparative Pharmacology.* (3, 1938)

Krop, Stephen, Ph.D. Yale University School of Medicine, 333 Cedar St., New Haven, Conn. *Instructor in Pharmacology.* (3, 1944)

Krueger, Albert Paul, M.D. Captain M.C., U.S.N.R. 3517 Life Sciences Bldg., University of California, Berkeley. *Professor of Bacteriology; Commanding Officer U.S.N. Medical Research Unit No. 1, Berkeley, Calif.* (4, 1930; 6, 1937)

Krueger, Hugo M., Ph.D. St. Louis University Medical School, 1402 S. Grand Blvd., St. Louis, Mo. *Associate Professor of Pharmacology.* (1, 1931; 3, 1935)

Krumbhaar, Edward B., M.D., Ph.D. University of Pennsylvania Medical School, Philadelphia. *Professor of Pathology.* (1, 1914; 4, prior to 1920)

Kruse, Harry Dayton, M.D., Sc.D. Milbank-Memorial Fund, 40 Wall St., New York City. (2, 1933)

Kruse, Theophile K., A.M., Ph.D. University of Pittsburgh Medical School, Pittsburgh, Pa. *Professor of Physiology and Pharmacology.* (1, 1919; 3, 1920)

Kubie, Lawrence S., M.D. 7 E. 81st St., New York City. *Associate in Neurology, College of Physicians and Surgeons, Columbia University.* (4, 1928)

Kuhn, Harry A., M.S. 3915 Fulton St., N.W., Washington, D. C. *Colonel, C. W. S., War Department; Executive Officer, C. W. Procurement District.* (3, 1927)

Kuhn, Ludwig R., Ph.D. 329 2nd St., Pitcairn, Pa. (6, 1939)

Kunde, Margarete M., Ph.D., M.D. 116 S. Michigan Ave., Chicago, Ill. *Instructor in Medicine, Northwestern University Medical School; Clinical Assistant in Endocrinology, Cook County Hospital* (1, 1924)

Kurtz, Alton C., Ph.D. Department of Biochemistry, Medical School, University of Oklahoma, Oklahoma City. *Assistant Professor.* (2, 1942)

Kydd, David M., M.D. Mary Imogene Bassett Hospital, Cooperstown, N. Y. *Associate Physician.* (5, 1934)

Kyes, Preston, A.M., Sc.D., M.D. North Jay, Me. (6, 1918)

Lacy, G. R., M.D. University of Pittsburgh, Pittsburgh, Pa. *Professor of Bacteriology and Immunology.* (4, 1927)

Lamb, Alvin R., M.S., Ph.D. Experiment Station, Hawaiian Sugar Planters' Association, Honolulu. *Research Associate.* (2, 1923; 5, 1934)

Lambert, Robert A., M.D. Rockefeller Foundation, 49 W. 49th St., New York City. *Associate Director for the Medical Sciences.* (4, 1922)

Lamport, Harold, M.D.* Yale University School of Medicine, New Haven, Conn. *Assistant Professor of Physiology.* (1, 1943)

Lamson, Paul Dudley, M.D. Vanderbilt University Medical School, Nashville, Tenn. *Professor of Pharmacology.* (1, 1921; 3, 1915)

Lamson, Robert W., A.M., Ph.D., M.D. Suite 810, 1930 Wilshire Blvd., Los Angeles, Calif. *Professor of Medicine and Public Health, University of Southern California School of Medicine.* (6, 1928)

Lancefield, Rebecca C., Ph.D. 4 Kenmore Rd., Douglaston, Long Island, N. Y. *Associate Member, Rockefeller Institute for Medical Research.* (6, 1933)

Landis, Carney, Ph.D. Psychiatric Institute and Hospital, Columbia University, 722 W. 168th St., New York City. *Principal Research Psychologist and Professor of Psychology.* (1, 1939)

Landis, Eugene Markley, Ph.D., M.D. Department of Physiology, Harvard Medical School, 25 Shattuck St., Boston, Mass. *George Higginson Professor of Physiology.* (1, 1928)

Lands, Alonzo M., M.A., Ph.D. Frederick Stearns and Co., 6533 Jefferson Ave., Detroit, Mich. *Director, Pharmacologic Research.* (1, 1942)

Lange, Carl, M.D. 371 Morris St., Albany, N. Y. *Associate Bacteriologist, Divisions of Laboratories and Public Health, New York State Department of Health.* (6, 1938)

Langley, Wilson D., Ph.D. University of Buffalo Medical School, Buffalo, N. Y. *Associate Professor of Biological Chemistry.* (2, 1937)

Langworthy, Orthello R., M.A., M.D. Johns Hopkins Hospital, Baltimore, Md. *Associate Professor of Neurology, Johns Hopkins University.* (1, 1928)

Larrabee, Martin G., Ph.D. Johnson Foundation, Hospital of University of Pennsylvania, Philadelphia. *Fellow in Medical Physics and Lecturer in Biophysics.* (1, 1940)

Larson, Edward, Ph.D. Temple University Medical School, Broad and Ontario Sts., Philadelphia, Pa. *Associate Professor of Pharmacology.* (1, 1929; 3, 1937)

Larson, Hardy W., A.M., Ph.D. Metropolitan Life Insurance Co., Biochemical Laboratory, 1 Madison Ave., New York City. *Research Chemist.* (2, 1937)

Larson, Paul S., Ph.D. Medical College of Virginia, Richmond. *Associate in Physiology and Pharmacology.* (1, 1939)

Larson, W. P., M.D. University of Minnesota, Minneapolis. *Professor and Head of Department of Bacteriology and Immunology.* (6, 1917)

Lashley, K. S., M.S., Ph.D., D.Sc. Yerkes Laboratories, Orange Park, Fla. *Research Professor of Neuropsychology, Harvard University; Director, Yerkes Laboratories of Primate Biology, Inc. Member of the National Academy of Sciences.* (1, 1923)

Laskowski, M., Ph.D. University of Arkansas, School of Medicine, Little Rock. *Associate Professor of Physiological Chemistry.* (2, 1944)

Laug, E. P., M.A., Ph.D. Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington 25, D. C. *Senior Pharmacologist.* (2, 1938)

Laurens, Henry, A.M., Ph.D., LL.D. School of Medicine, Tulane University, Station 20, New Orleans, La. *Professor of Physiology.* (1, 1913)

Lavine, T. F., Ph.D. Lankenau Hospital Research Institute, Philadelphia, Pa. *Research Chemist.* (2, 1938)

Lawrence, W. Sherwood, M.D. Dept. of Pharmacology, University of Michigan, Ann Arbor. *Instructor of Pharmacology.* (3, 1944)

Lawson, Hampden, M.D., Ph.D. University of Louisville, Louisville, Ky. *Professor of Physiology.* (1, 1933)

Leake, Chauncey D., M.S., Ph.D. The University of Texas Medical Branch, Galveston. *Vice-President of the University of Texas in Charge of the Medical Program.* (1, 1923; 3, 1924)

Leathes, John Beresford, M.A., M.B., F.R.C.S., F.R.S. 106 Banbury Rd., Oxford, England. (2, 1909)

Lederer, Ludwig George, Ph.D., M.D. Pennsylvania Central Airlines, National Airport, Washington, D. C. *Medical Director.* (1, 1940)

Lederer, Max, M.D. 1037 President St., Brooklyn, N. Y. *Director of Laboratories, Jewish Hospital.* (6, 1920)

Lee, Milton O., M.A., Ph.D. Harvard Medical School, Boston, Mass. *Associate, Memorial Foundation for Neuro-endocrine Research; Research Fellow in Physiology.* (1, 1927; 5, 1933)

Lee, Robert Cleveland, B.Ch.E., M.A.* 309 Bellevue St., Newton, Mass. *Member of Research Staff, Nutrition Lab., Carnegie Institution of Washington.* (1, 1944; 5, 1940)

Leese, Chester E., M.S., Ph.D. George Washington University School of Medicine, Washington, D. C. *Associate Professor of Physiology.* (1, 1934)

Lehman, Arnold J., Ph.D., M.D. University of North Carolina School of Medicine, Chapel Hill. *Professor of Pharmacology.* (3, 1937)

Lehman, Robert A., M.S., Ph.D. New York University College of Medicine, 477 First Ave., New York City. *Instructor in Therapeutics.* (3, 1942)

Lehmann, Gerhard, M.D., Dr. Ing. University of Louisville School of Medicine, Louisville, Ky. *Associate Professor of Pharmacology.* (3, 1939)

Lenhart, Carl H., M.D. Lakeside Hospital, 2065 Adelbert Rd., Cleveland, O. *Oliver H. Payne Professor of Surgery, Western Reserve University.* (1, 1921)

Lennette, Edwin H., Ph.D., M.D. 49 W. 49th St. New York, N. Y. *Staff Member, International Health Division, The Rockefeller Foundation.* (4, 1941)

Leonard, Clifford Shattuck, M.S., Ph.D. University of Vermont Medical College, Burlington. *Assistant Professor of Pharmacology.* (3, 1927)

Lepkovsky, Samuel, M.S., Ph.D. University of California, Berkeley. *Associate Professor of Poultry Husbandry.* (2, 1933; 5, 1933)

L'Esperance, Elise L., M.D. 321 E. 15th St., New York City. *Director of Laboratories, New York Infirmary for Women and Children.* (6, 1920)

Leverton, Ruth M., Ph.D. Department of Home Economics, University of Nebraska, Lincoln. *Associate Professor Human Nutrition Research.* (5, 1942)

Levin, Isaac, M.D. 57 W. Fifty-seventh St., New York City. *Clinical Professor of Cancer Research, New York University; Chief of the Department of Cancer Service, Montefiore Hospital; Director, New York City Cancer Institute.* (1, 1900)

Levin, Louis, Ph.D. 630 W. 168th St., New York City. *Research Associate in Biochemistry, Assigned to Anatomy, College of Physicians and Surgeons, Columbia University.* (2, 1939)

Levine, Harold, Ph.D. Pabst Brewing Co., 917 W. Juneau Ave., Milwaukee, Wis. *Biochemist.* (2, 1933; 5, 1933)

Levine, Milton, M.S., Ph.D. The Harrower Laboratory, Inc., Glendale, Calif. (6, 1942)

Levine, Philip, M.D., M.A. Newark Beth Israel Hospital, 201 Lyons Ave., Newark, N. J. *Serologist and Bacteriologist.* (6, 1925)

Levine, Rachmiel, M.D., C.M. Michael Reese Hospital, Chicago, Ill. *Acting Director, Department of Metabolic Research.* (1, 1942)

Levine, Samuel Z., M.D., New York Hospital, 525 E. 68th St., New York City. *Professor of Pediatrics, Cornell University Medical College; Pediatrician-in-Chief, New York Hospital.* (5, 1933)

Levine, Victor Emanuel, A.M., Ph.D., M.D. Creighton University School of Medicine, Omaha, Neb. *Professor of Biological Chemistry and Nutrition.* (2, 1936)

Levinson, Samuel A., M.D. University of Illinois College of Medicine, 808 S. Wood St., Chicago. *Professor of Pathology; Director Laboratories, Research & Educational Hospital.* (1938)

Levison, Louis A., M.D. 421 Michigan St., Toledo, O. *Physician to Toledo Hospital; Physician to St. Vincent Hospital.* (6, 1916)

Levy, Milton, Ph.D. 477 First Ave., New York City. *Assistant Professor of Chemistry, New York University College of Medicine.* (2, 1933)

Levy, Robert L., M.D. 730 Park Ave., New York City. *Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University.* (3, 1915)

Lewey, F. H., M.D. University Hospital, University of Pennsylvania, Philadelphia. *Visiting Professor of Neurophysiology and Consultant in Neurology. Major (MC), AUS.* (1, 1937)

Lewis, Howard Bishop, Ph.D. Medical School, University of Michigan, Ann Arbor. *Professor of Biological Chemistry and Director of the College of Pharmacy.* (1, 1925; 2, 1913; 5, 1933)

Lewis, Julian Herman, M.D. 4750 Champlain Ave., Chicago, Ill. *Associate Professor*

Pathology, University of Chicago; Member of the Otho S. A. Sprague Memorial Institute. (4, 1924)

Lewis, Robert C., Ph.D. 4200 E. 9th Ave., Denver, Colo. *Professor of Biochemistry, School of Medicine, University of Colorado.* (2, 1931; 5, 1933)

Lewis, Warren H., M.D. The Wistar Institute of Anatomy and Biology, Woodland Ave. and 36th St., Philadelphia, Pa. *Member; Member of the National Academy of Sciences.* (1, 1919)

Li, Choh Hao, Ph.D. 4596 Life Science Bldg., University of California, Berkeley. *Research Associate and Lecturer.* (2, 1944)

Li, Richard D., M.D. Peiping Union Medical College, Peiping, China. *Instructor in Pharmacology.* (3, 1941)

Libby, Raymond L., M.S., Ph.D. American Cyanamid Co., 1937 W. Main St., Stamford, Conn. *Bio-physicist.* (6, 1938)

Libet, Benjamin, Ph.D. Personal Equipment Section, Army Air Forces, Materiél Command, Wright Field, Dayton. O. (1, 1942)

Libman, Emanuel, M.D. 180 E. 64th St., New York City. *Consulting Physician, Mount Sinai Hospital.* (6, 1920)

Liddell, Howard S., A.M., Ph.D. Cornell University, Ithaca, N. Y. *Professor of Psychology.* (1, 1925)

Lieb, Charles C., M.D. 630 W. 168th St., New York City. *Hosack Professor of Pharmacology, College of Physicians and Surgeons, Columbia University.* (1, 1936; 3, 1915)

Lieberman, Arnold L., M.D., Ph.D. 738 Broadway, Suite 502, Gary, Ind. *Assistant in Medicine, Northwestern University.* (1, 1934)

Lifson, Nathan, M.D., Ph.D.* 617 Kenwood Parkway, Minneapolis, Minn. *Assistant Professor of Physiology, University of Minnesota Medical School.* (1, 1944)

Lightbody, Howard D., M.S., Ph.D. Western Regional Research Laboratory, U. S. Department of Agriculture, Albany 6, Calif. *Principal Biochemist.* (2, 1936)

Lillie, Ralph Stayner, Ph.D., Sc.D. University of Chicago, Chicago, Ill. *Professor Emeritus of General Physiology; Physiologist, Marine Biological Laboratory, Woods Hole, Mass.* (1, 1905; 2, 1913)

Lillie, R. D., M.D. Chief Pathology Laboratory, National Institute of Health, Bethesda, Md. *Senior Surgeon, U.S.P.H.S.* (4, 1941)

Lim, Robert Kho-Seng, Ph.D., D.Sc., F.R.S.E. Board of Health, Chinese National Government, Chunking, China. (1, 1923)

Lindsley, Donald B., M.A., Ph.D. Bradley Home, East Providence, R.I. *Director of Psychological and Neurophysiological Laboratory; Assistant Professor of Psychology, Brown University. Director, N.D.R.C. project, Camp Murphy, Fla.* (1, 1937)

Linegar, Charles R., Ph.D. E. R. Squibb and Sons, Biological Laboratory, New Brunswick, N. J. *Chief, Biological Development and Control Laboratory.* (3, 1938)

Lineweaver, Hans, M.A., Ph.D. Western Regional Research Laboratory, U. S. Department of Agriculture, Albany 6, Calif. *Senior Biochemist.* (2, 1941)

Link, Karl Paul, Ph.D. Biochemistry Building, University of Wisconsin, Madison. *Professor of Biochemistry.* (2, 1931)

Lintz, William, M.D. 36 Plaza St., Brooklyn, N. Y. *Late Professor of Immunology and Bacteriology and Clinical Professor of Medicine, Long Island College of Medicine.* (6, 1920)

Lipman, Mrs. Miriam O., A.M. Presbyterian Hospital, 620 W. 168th St., New York City. *Research Assistant, Edward Daniels Faulkner Arthritis Clinic.* (6, 1931)

Lipmann, Fritz, M.D., Ph.D. Biochemical Research Laboratory, Massachusetts General Hospital, Boston. *Research Chemist; Head, Biochemical Research Laboratory; Research Fellow in Biochemistry and Surgery, Harvard Medical School.* (2, 1941)

Litchfield, John T., Jr., M.D. University of Minnesota Medical School, Minneapolis, 14. *Assistant Professor of Pharmacology.* (3, 1940)

Little, James Maxwell, M.S., Ph.D. Bowman Gray School of Medicine of Wake Forest College, Winston-Salem, N. C. *Assistant Professor of Physiology and Pharmacology.* (1, 1942)

Livingston, Alfred E., Ph.D. Temple University School of Medicine, Philadelphia, Pa. *Professor of Pharmacology.* (1, 1917; 3, 1920)

Lloyd, David P. C., D.Ph. Laboratory of Physiology, Yale University School of Medicine, 333 Cedar St., New Haven, Conn. *Assistant Professor of Physiology.* (1, 1939)

Locke, Arthur P., Ph.D. Zonite Products Corporation, New Brunswick, N. J. *Chief Research Chemist.* (6, 1926)

Lodholz, Edward, M.D. Medical Laboratories, University of Pennsylvania, Philadelphia. *Isaac Ott Professor of Physiology, Graduate School of Medicine.* (1, 1913)

Loeb, Leo, M.D. Washington University Medical School, St. Louis, Mo. *Professor Emeritus of Pathology; Member, National Academy of Sciences.* (1, 1907; 4, 1913)

Loebel, Robert O., M.D. Russell Sage Institute of Pathology, Cornell Medical College, 1300 York Ave., New York City. *Research Fellow; Adjunct Assistant Visiting Physician, Second (Cornell) Medical Division of Bellevue Hospital.* (1, 1928)

Loew, Earl R., M.S., Ph.D. 7415 Woodrow Wilson, Detroit, Mich. *Research Pharmacologist, Parke, Davis & Co.; Lecturer in Physiology, Wayne University College of Medicine.* (1, 1940)

Loewe, W. S., M.D. 17 Cole Terrace, New Rochelle, N. Y. *Hon. Prof. Pharmacology, Heidelberg; Dept of Pharmacology, Cornell University Medical College.* (3, 1936)

Logan, Milan A., Ph.D. University of Cincinnati School of Medicine, Cincinnati, O. *Professor of Biological Chemistry.* (2, 1936)

Long, C. N. H., M.Sc., D.Sc., M.D. Yale University, New Haven, Conn. *Sterling Professor of Physiological Chemistry.* (1, 1935; 2, 1927)

Long, Esmond R., M.D. 7th and Lombard Sts., Philadelphia, Pa. *Director, Henry Phipps Institute; Professor of Pathology, University of Pennsylvania.* (4, 1930)

Long, Perrin Hamilton, M.D. The Johns Hopkins University, 615 N. Wolfe St., Baltimore, Md. *Professor of Preventive Medicine; Colonel, M.C.* (3, 1940)

Longcope, Warfield T., M.D. Johns Hopkins Hospital, Baltimore, Md. *Professor of Medicine, Johns Hopkins University.* (3, 1921; 4, 1913; 6, 1923)

Longenecker, Herbert Eugene, M.S., Ph.D. Department of Chemistry, University of Pittsburgh, Pittsburgh, Pa. *Dean of Research in the Natural Sciences and Professor of Biochemistry.* (2, 1940)

Looney, Joseph Michael, M.D. 383 M. C. Det., Camp Ellis, Ill. *Chief of Special Service, Major, U. S. Army.* (2, 1922)

Loosli, Clayton Garr, M.D. The University of Chicago, Department of Medicine, Chicago, Ill. *Assistant Professor.* (4, 1940)

Loosli, J. K., M.S., Ph.D. Animal Nutrition Laboratory, Cornell University, Ithaca, N. Y. *Assoc. Prof. of Animal Nutr. and Assoc. Animal Nutritionist in Exp. Sta.* (5, 1944)

Lorber, Victor, M.D., Ph.D* 1901 East River Terrace, Minneapolis, Minn. *Instructor in Physiology, University of Minnesota Medical School.* (1, 1944)

Lorente de Nó, Rafael, M.D. The Rockefeller Institute for Medical Research, 66th St. and York Ave., New York City. *Member.* (1, 1937)

Lorenz, Egon, Ph.D. National Cancer Institute, Bethesda, Md. *Senior Biophysicist.* (4, 1942)

Loring, H. S., M.S., Ph.D. Stanford University, Calif. *Associate Professor of Biochemistry.* (2, 1938)

Lothrop, Alfred P., M.A., Ph.D. 279 Elm St., Oberlin, O. *Professor of Organic Chemistry, Oberlin College.* (2, 1912)

Loveless, Mary H., M.D. New York Hospital, 525 E. 68th St., New York City. *Research Associate, Cornell Medical School; Physician to Out-Patients, New York Hospital.* (6, 1941)

Lowell, Francis C., M.D. Nine Acre Corner, Concord, Mass. *Instructor in Medicine, Boston City Hospital.* (6, 1942)

Lowry, Oliver H., M.D., Ph.D. Research Laboratory, Public Health Research Institute of the City of New York, Foot of E. 15th St. *Research Associate.* (2, 1942)

Lubinski, Herbert, M.D. Jewish General Hospital, 3755 St. Catherine Rd., Montreal, Canada. *Bacteriologist.* (6, 1941)

Lucas, George H. W., M.A., Ph.D. University of Toronto, Toronto, Canada. *Associate Professor of Pharmacology.* (2, 1925; 3, 1928)

Luck, James Murray, Ph.D. Stanford University, Stanford, Calif. *Professor of Biochemistry.* (2, 1925)

Lucké, Balduin, M.D. 141 Montgomery Ave., Bala-Cynwyd, Pa. *Professor of Pathology, University of Pennsylvania Medical School.* (4, 1924)

Luckhardt, Arno Benedict, M.S., Ph.D., M.D. University of Chicago, Chicago, Ill. *Professor of Physiology.* (1, 1911)

Ludewig, Stephan, Ph.D. University of Virginia School of Medicine, University. *Assistant Professor of Biochemistry.* (2, 1941)

Luduena, Froilan P., Ph.D., M.D. Department of Pharmacology, Stanford University Medical School, San Francisco, Calif. *Assistant Professor of Pharmacology.* (3, 1941)

Lukens, Francis D. W., M.D. University of Pennsylvania, 809 Maloney Clinic, 36th and Spruce Sts., Philadelphia. *Assistant Professor of Medicine and Director, George S. Cox Medical Research Institute.* (1, 1938)

Lund, E. J., Ph.D. Department of Zoology and Physiology, University of Texas, Austin. *Professor of General Physiology.* (1, 1930)

Lundgren, Harold P., Ph.D. Western Regional Research Laboratory, U.S.D.A., Albany 6, Calif. *Chemist.* (2, 1942)

Lundy, John Silas, M.D. The Mayo Foundation, Rochester, Minn. *Chief of Section on Anesthesia.* (3, 1935)

Lurie, Max B., M.D. Henry Phipps Institute, 7th and Lombard Sts., Philadelphia, Pa. *Assistant Professor of Experimental Pathology.* (4, 1934; 6, 1930)

Lutz, Brenton R., Ph.D. Boston University, 688 Boylston St., Boston, Mass. *Professor of Biology.* (1, 1925)

Luyet, Basile J., Sc.D. (Biol.), Sc.D. (Physics). St. Louis University School of Medicine, St. Louis, Mo. *Professor of Biology.* (1, 1936)

Lyall, Harold W., A.M., Ph.D. Division of Laboratories and Research, New York State Depart-

ment of Health, Albany. *Assistant Director in charge of Antitoxin, Serum, and Vaccine Laboratories.* (6, 1937)

Lyman, Carl M., Ph.D. Division of Swine Husbandry, Agricultural Experiment Station, College Station, Texas. *Nutritionist.* (2, 1940)

Lyman, John F., Ph.D. Townshend Hall, Ohio State University, Columbus. *Professor of Agricultural Chemistry.* (2, 1920; 5, 1933)

Macallum, A. Bruce, M.D., Ph.D. Medical School, University of Western Ontario, London, Ont., Canada. *Professor of Biochemistry.* (2, 1914)

MacArthur, Edith H., A.M., Ph.D. Skidmore College, Saratoga Springs, N. Y. *Professor and Director of Home Economics.* (5, 1933)

MacCorquodale, D. W., M.S., Ph.D. Abbott Laboratories, North Chicago, Ill. *Head, Biochemical Research.* (2, 1934)

MacFadyen, Douglas A., M.A., M.D. Box 7, Room 103, Army Medical School, Army Medical Center, Washington, D. C. *Captain, U. S. Army.* (2, 1942)

MacKay, Eaton M., M.D. The Scripps Metabolic Clinic, La Jolla, Calif. (1, 1930)

Mackenzie, Cosmo G., D.Sc. The Johns Hopkins University, Baltimore, Md. *Associate in Biochemistry, School of Hygiene and Public Health.* (5, 1942)

Mackenzie, George M., M.D. Mary Imogene Bassett Hospital, Cooperstown, N. Y. *Physician-in-Chief; Director, Otsego County Laboratories.* (6, 1921)

MacLeod, Colin M., M.D. New York University College of Medicine, 477 First Ave., New York City. *Professor of Bacteriology.* (6, 1937)

MacLeod, Florence L., M.A., Ph.D. University of Tennessee, Knoxville. *Professor of Nutrition.* (2, 1927; 5, 1933)

MacLeod, Grace, M.A., Ph.D. 106 Morningside Drive, New York City. *Professor Emeritus of Nutrition, Teachers College, Columbia University.* (2, 1924; 5, 1933)

MacLeod, John, M.S., Ph.D. Cornell University Medical College, 1300 York Ave., New York City. *Research Associate of Anatomy.* (1, 1942)

MacNabb, Andrew L., V.S., B.V.Sc., F.A.P.H.A. Department of Health of Ontario, Toronto, Canada. *Director of Laboratories.* (6, 1941)

MacNeal, Ward J., M.D. New York Post-Graduate Medical School and Hospital, 303 E. 20th St., New York City. *Professor of Bacteriology.* (4, 1925)

MacNider, William deB., M.D., Sc.D., LL.D. University of North Carolina, Chapel Hill. *Kenan Research Professor of Pharmacology; Member, National Academy of Sciences.* (1, 1912; 2, 1912; 3, 1909; 4, prior to 1920)

Macht, David Israel, M.D., Phar. D. (hon.), Litt. D. 3420 Auchentoroly Ter., Baltimore, Md. *Director of Pharmacological Research Laboratory, Hynson, Westcott and Dunning, Inc.; Professorial Lecturer in Physiology, Yeshiva College, New York City.* (1, 1916)

Madden, Sidney C., M.D. University of Rochester School of Medicine and Dentistry, Rochester, N. Y. *Assistant Professor of Pathology.* (4, 1939)

Maddock, Stephen, M.D. Boston City Hospital, Boston, Mass. *Director of Surgical Research Laboratory.* (4, 1931)

Madsen, Louis L., Ph.D. Bureau of Animal Industry, U. S. Department of Agriculture, Box 71, Berwyn, Md. *Nutritionist.* (5, 1940)

Maes, Julian P., M.D.* Dartmouth Medical School, Hanover, N. H. *Department of Pharmacology.* (1, 1943)

Magath, Thomas B., M.S., Ph.D., M.D. Mayo Clinic, Rochester, Minn. *Associate Professor of Clinical Bacteriology and Parasitology, University of Minnesota, Mayo Foundation; Consultant Physician in Clinical Laboratories, Mayo Clinic.* (1, 1928)

Magill, Thomas P., M.D. Cornell University Medical College, 1300 York Ave., New York City. (6, 1937)

Magoun, Horace W., Ph.D. Northwestern University Medical School, 303 E. Chicago Ave., Chicago, Ill. *Professor of Microscopic Anatomy.* (1, 1937)

Mahon, Eleanor Conway, Ph.D. Iron River, Mich. (4, 1940)

Main, Rolland J., Ph.D. Medical College of Virginia, Richmond. *Professor of Physiology.* (1, 1936)

Maison, George L., M.S., M.D. Aero-Medical Research Laboratory, Engineering Division, Wright Field, Dayton, O. *1st. Lt., Medical Corps., Assistant Professor of Physiology, Wayne University, Detroit, Mich.* (1, 1939)

Major, Randolph T., M.Sc., Ph.D. Coles Ave., Mountainside, Westfield, N. J. *Director of Research, Merck & Co., Inc., Rahway, N. J.* (2, 1942)

Mallory, G. Kenneth, M.D. Mallory Institute of Pathology, Boston City Hospital, Boston, Mass. *Associate Professor.* (4, 1940)

Mallory, Tracy B., M.D. Massachusetts General Hospital, Boston. *Chief of Pathology and Bacteriology; Assistant Professor of Pathology, Harvard Medical School.* (4, 1937)

Maloney, Arnold H., Ph.D., M.D., LL.D. Howard University School of Medicine, Washington, D. C. *Professor and Head of Department of Pharmacology.* (3, 1932)

Maltaner, Frank, Ph.D. 388 New Scotland Ave., Albany, N. Y. *Associate Biochemist, Division of Laboratories and Research, New York State Department of Health.* (6, 1920)

Maluf, N. S. Rustum, M.S., Ph.D. Company D, SCSU, No. 1144, 427 Vanderbilt Hall, Harvard School, Boston, Mass. (1, 1942)

Man, Evelyn B., Ph.D. 333 Cedar St., New Haven, Conn. *Assistant Professor in the Biochemistry Laboratory, Yale University School of Medicine.* (2, 1936)

Manery, Jeanne Forest, M.A., Ph.D. Medical School, University of Toronto, Toronto, Ont., Canada. *Demonstrator in Biochemistry.* (1, 1937)

Mann, Frank C., M.A., M.D., Sc.D., LL.D. Mayo Clinic, Box 256, Rochester, Minn. *Director, Division of Experimental Medicine; Professor of Experimental Medicine, Mayo Foundation.* (1, 1916; 3, 1923; 4, 1924)

Manning, G. W., M.D.* 20 Woodington Ave., Toronto, Ontario, Canada. *Medical Officer in Charge, No. 2 R.C.A.F. Research Unit.* (1, 1944)

Manville, Ira Albert, M.A., M.D., Ph.D. University of Oregon Medical School, Portland. *Associate Clinical Professor of Medicine and Director of Nutritional Research Laboratories.* (1, 1933)

Manwaring, Wilfred H., M.D. Stanford University, Palo Alto, Calif. *Professor Emeritus of Bacteriology and Experimental Pathology.* (4, prior to 1920; 6, 1917)

Marine, David, A.M., M.D. Montefiore Hospital, Gunhill Road and East 210th St., New York City. *Director of Laboratories.* (1, 1910; (4, 1913)

Markowitz, J., M.D., Ph.D. 220 Bloor St., Toronto, Ont., Canada. *Research Associate in Physiology, University of Toronto, Faculty of Medicine.* (1, 1929)

Marmont, George H., Ph.D. 4855 Fourth Ave., Detroit, Mich. *Electronic Engineer, Bendix Aviation Research Laboratories.* (1, 1941)

Marmorston, Jessie. 522 Genesee, Los Angeles, Cal. (6, 1932)

Marrazzi, Amedeo S., M.D. Wayne University College of Medicine, Detroit 26, Mich. *Professor and Head of the Department of Pharmacology.* (3, 1938)

Marsh, Gordon, Ph.D.* State University of Iowa, Iowa City. *Assistant Professor of Zoology.* (1, 1944)

Marsh, M. Elizabeth, M.S., Ph.D. Killian Research Laboratories, 49 W. 45th St., New York City. *Assistant Director.* (1, 1929; 5, 1933)

Marshak, Alfred George, M.A., Ph.D. Radiation Laboratory, University of California, Berkeley. *Research Associate and Finney-Howell Fellow.* (1, 1940)

Marshall, Eli Kennerly, Jr., Ph.D., M.D., LL.D. Johns Hopkins Medical School, Baltimore, Md. *Professor of Pharmacology and Experimental Therapeutics; Member, National Academy of Sciences.* (1, 1915; 2, 1913; 3, 1915)

Marshall, Wade H., Ph.D. 9700 Brunett Ave., Silver Spring, Md. Wilmer Ophthalmological Institute, Johns Hopkins Hospital, Baltimore, Md. *Associate in Physiological Optics, Johns Hopkins Hospital.* (1, 1937)

Martin, Arthur W., Jr., Ph.D.* 202 Physiology Hall, University of Washington, Seattle. *Associate Professor of Animal Biology.* (1, 1944)

Martin, Donald S., M.D. Duke Hospital, Durham, N. C. *Associate Professor of Bacteriology and Associate in Medicine, Duke University School of Medicine.* (4, 1940; 6, 1943)

Martin, Stevens J., M.A., Ph.D. Tilton General Hospital, Fort Dix, N. J. *Capt. M. C., Chief of Sections on Anesthesia and Operating Pavilion, and Resuscitation and Oxygen Therapy.* (1, 1933)

Mason, Edward C., M.D., Ph.D. University of Oklahoma School of Medicine, Oklahoma City. *Professor of Physiology.* (1, 1935)

Mason, H. L., M.A., Ph.D. Mayo Clinic, Rochester, Minn. *Associate Professor of Physiological Chemistry, The Mayo Foundation, University of Minnesota.* (2, 1941)

Mason, Karl Ernest, Ph.D. The University of Rochester, School of Medicine and Dentistry, Rochester, N. Y. *Professor of Anatomy.* (1, 1932; 5, 1941)

Mason, Morton F., Ph.D. Parkland Hospital, Oak Lawn Ave., Dallas, Texas. *Professor of Pathological Chemistry and Experimental Medicine, Southwestern Medical College.* (2, 1938)

Massengale, Oliver N., Ph.D. Mead Johnson & Co., Research Laboratory, Evansville, Ind. *Research Biochemist.* (2, 1937)

Masson, Georges M. C., Ph.D.* McGill University, Montreal, Canada. *Research Associate.* (1, 1944)

Mast, S. O., Ph.D. Johns Hopkins University, Baltimore, Md. *Professor of Zoology.* (1, 1920)

Mathews, Albert Prescott, Ph.D., D.Sc. (hon.). Woods Hole, Mass. *Professor Emeritus of Biochemistry, Univ. of Cincinnati.* (1, 1898; 2, 1906)

Mattill, Henry A., A.M., Ph.D. State University of Iowa, Iowa City. *Professor of Biochemistry.* (1, 1913; 2, 1909; 5, 1933)

Maurer, Frank W., Ph.D. Harvard School of Public Health, 55 Shattuck St., Boston, Mass. *Assistant Professor of Physiology.* (1, 1941)

Mavor, James Watt, Ph.D. Union College, Schenectady, N. Y. *Professor of Biology.* (1, 1930)

Mayerson, Hymen S., Ph.D. Tulane University School of Medicine, Station 20, New Orleans, La. *Associate Professor of Physiology.* (1, 1928)

Maynard, Leonard A., Ph.D. Cornell University, Ithaca, N. Y. *Professor of Animal Nutrition; Director of United States Soil, Plant and Nutrition Laboratory; Member National Academy of Sciences.* (2, 1930; 5, 1933)

Mazur, Abraham, M.A., Ph.D. Medical Research Laboratory, Edgewood Arsenal, Md. *Captain, Sanitary Corps, U. S. Army; Instructor, Department of Chemistry, City College of New York (on leave).* (2, 1944)

McCann, William S., M.D., D.Sc. (Hon.) USS Refuge AH-11, Fleet P.O., New York. *Captain (MC) USNR. The Charles A. Dewey Professor of Medicine, University of Rochester, School of Medicine. (On leave.)* (2, 1923; 5, 1933)

McCarrell, Jane D., M.A., Ph.D. Dept. Surgical Research, Massachusetts General Hospital, Boston. *Research Fellow in Anesthesia, Massachusetts General Hospital; Instructor in Physiology, Harvard School of Public Health.* (1, 1942)

McCawley, Elton Leeman, Ph.D. Yale Medical School, New Haven, Conn. *Instructor in Pharmacology.* (3, 1944)

McCay, Clive M., M.S., Ph.D. Animal Nutrition Laboratory, Cornell University, Ithaca, N. Y. *Professor of Animal Nutrition.* (2, 1929; 5, 1933)

McChesney, Evan William, Ph.D.* Winthrop Chemical Co., 33 Riverside Ave. Rensselaer, N. Y. *Research Biochemist.* (1, 1944)

McClellan, Walter S., M.D. Saratoga Spa, Saratoga Springs, N. Y. *Medical Director; Associate Professor of Medicine, Albany Medical College.* (1, 1931)

McClendon, J. F., M.S., Ph.D. Route 1, Trooper Road, Norristown, Pa. *Research Professor of Physiology, Hahnemann Medical College.* (1, 1910; 2, 1914; 5, 1935)

McClosky, William T., B.A. 5120 7th St., N.W., Washington, D. C. *Senior Pharmacologist, Div. of Pharmacology, Food and Drug Administration.* (3, 1929)

McCollum, Elmer Verner, M.A., Ph.D., Sc.D., LL.D. Johns Hopkins University, School of Hygiene and Public Health, 615 N. Wolfe St., Baltimore, Md. *Professor of Biochemistry; Member, National Academy of Sciences.* (2, 1910; 5, 1933)

McCouch, Grayson Prevost, M.D. University of Pennsylvania, Philadelphia. *Assistant Professor of Physiology.* (1, 1925)

McCrea, Forrest D., Ph.D. Duke University School of Medicine, Durham, N. C. *Associate Professor of Physiology and Pharmacology.* (1, 1929; 3, 1937)

McCrudden, F. H., M.D. 501 Boylston St., Boston, Mass. *Assistant Medical Director, New England Mutual Life Insurance Co.* (2, 1906)

McCullagh, D. Roy, M.Sc. (Man.); Ph.D. (Cantab.), FIC. 150 Northfield Rd., Bedford, O. *Vice-President.* (2, 1932)

McCulloch, Warren Sturgis, M.A., M.D. University of Illinois, College of Medicine, Chicago. *Associate Professor of Psychiatry.* (1, 1936)

McCutcheon, Morton, M.D. University of Pennsylvania Medical School, Philadelphia. *Professor of Pathology.* (4, 1925)

McDonald, Francis Guy, M.S., Ph.D. Research Laboratory, Mead Johnson & Co., Evansville, Ind. *Research Biochemist.* (2, 1936)

McElroy, L. W. Dept. of Animal Science, University of Alberta, Edmonton, Canada. *Assist. Prof. of Animal Husbandry.* (5, 1944)

McElroy, William Swindler, M.D. School of Medicine, University of Pittsburgh, Pittsburgh, Pa. *Professor of Physiological Chemistry; Dean, School of Medicine.* (2, 1919)

McFarland, Ross A.,* Ph.D. Harvard University, Division of Industrial Research, Graduate School of Business Administration, Soldiers Field, Boston, Mass. *Assistant Professor of Industrial Research.* (1, 1943)

McFarlane, William Douglas, Ph.D. Macdonald College, (McGill University), Macdonald College, P. Q., Canada. *Professor of Chemistry.* (2, 1933)

McGinty, Daniel A., M.A., Ph.D. Parke, Davis & Co., Detroit, Mich. *Research Physiologist.* (1, 1925)

McGuigan, Hugh Alister, Ph.D., M.D. 1853 W. Polk St., Chicago, Ill. *Professor of Pharmacology and Therapeutics, College of Medicine, University of Illinois.* (1, 1907; 2, 1906; 3, 1913)

McHargue, J. S., M.S., Ph.D., D.Sc. Department of Chemistry, Kentucky Agricultural Experiment Station, University of Kentucky, Lexington. *Emeritus Member.* (2, 1927)

McHenry, E. W., M.A., Ph.D., F.R.S.C. School of Hygiene, University of Toronto, Toronto, Canada. *Assistant Director, Connaught Laboratories; Associate Professor in Charge of Nutrition.* (2, 1938; 5, 1935)

McIntyre, A. R., Ph.D., M.D. College of Medicine, University of Nebraska, 42nd and Dewey Ave., Omaha. *Professor of Physiology and Pharmacology.* (1, 1933; 3, 1938)

McKee, Clara M., Squibb Institute for Medical Research, New Brunswick, N. J. *Assistant in Microbiology.* (6, 1941)

McLain, Paul L., M.D. University of Pittsburgh Medical School, Pittsburgh, Pa. *Assistant Professor of Physiology and Pharmacology; Major, M.C.* (3, 1940)

McLean, Franklin C., Ph.D., M.D. University of Chicago, Chicago, Ill. *Professor of Pathological Physiology.* (1, 1914; 2, 1916; 3, 1916)

McLester, James S., M.D., LL.D. University of Alabama, 930 S. 20th St., Birmingham. *Professor of Medicine.* (5, 1933)

McMaster, Philip D., M.D. The Rockefeller Institute for Medical Research, 66th St. and York Ave., New York City. (4, 1924)

McMeekin, Thomas L., Ph.D. Eastern Regional Research Laboratory, U. S. Department of Agriculture, Philadelphia, Pa. *Senior Chemist.* (2, 1935)

McNaught, James Bernard, M.D. Stanford University School of Medicine, San Francisco, Calif. *Associate Professor of Pathology.* (4, 1936)

McPhail, Murchie Kilburn, Ph.D. Dalhousie University, Halifax, Nova Scotia. *Professor of Pharmacology.* (3, 1941)

McQuarrie, Irvine, Ph.D., M.D. University of Minnesota, Minneapolis. *Professor and Head of Department of Pediatrics.* (4, 1927; 5, 1933)

Medes, Grace, Ph.D. Lankenau Hospital Research Institute, Philadelphia, Pa. *Research Physiological Chemist.* (2, 1930)

Medlar, Edgar M., M.D. Path. Bldg., Room 708 Bellevue Hospital, 1st Ave. at 26th St., New York, N. Y. *Pathologist.* (4, 1927)

Meek, Walter J., Ph.D. University of Wisconsin, Madison. *Professor of Physiology; Assistant Dean of the Medical School.* (1, 1908)

Mellon, Ralph R., M.D., M.Sc., Dr. P.H., Sc.D. (hon.). Institute of Pathology, Western Pennsylvania Hospital, Pittsburgh. *Director.* (6, 1918)

Melnick, Daniel, Ph.D. Food Research Laboratories, Inc., 48–14 33rd St., Long Island City, N. Y. *Chief Chemist.* (2, 1940; 5, 1942)

Melville, Kenneth Ivan, M.Sc., M.D., C.M. McGill University, Montreal, Canada. *Assistant Professor of Pharmacology.* (3, 1931)

Mendenhall, Walter L., S.M., M.D. Boston University Medical School, 80 E. Concord St., Boston, Mass. *Professor of Pharmacology.* (1, 1915; 3, 1917)

Mendez, Rafael, M.D. Loyola University School of Medicine, 706 S. Wolcott Ave., Chicago, Ill. *Assistant Professor of Pharmacology.* (3, 1944)

Menkin, Valy, M.A., M.D. Dept. of Pathology, Duke University School of Medicine, Durham, N. C. *Assistant Professor of Pathology.* (1, 1932; 4, 1932; 6, 1931)

Menten, Maud L., M.D., Ph.D. University of Pittsburgh, Pittsburgh, Pa. *Associate Professor of Pathology.* (1, 1915; 4, 1927)

Mettler, Fred A., A.M., Ph.D., M.D. Department of Neurology, College of Physicians and Surgeons, Columbia University, New York City. *Associate Professor of Anatomy.* (1, 1937)

Meyer, Curtis E., M.S., Ph.D. The Upjohn Co., Kalamazoo, Mich. *Research Chemist.* (2, 1942)

Meyer, Karl, M.D., Ph.D. 630 W. 168th St., New York City. *Associate Professor of Bio-Chemistry, Dept. of Ophthalmology, College of Physicians and Surgeons, Columbia University.* (2, 1934)

Meyer, Karl F., M.D., Ph.D. Medical Center, San Francisco, Calif. *Professor of Bacteriology, University of California. Director of the George Williams Hooper Foundation for Medical Research.* (4, 1930; 6, 1922)

Meyerhof, Otto, M.D., LL.D. Department of Physiological Chemistry, University of Pennsylvania School of Medicine, Philadelphia. *Research Professor of Biochemistry.* (2, 1941)

Michaelis, Leonor, M.D. Rockefeller Institute for Medical Research, 66th St. and York Ave., New York City. *Member Emeritus.* (2, 1929)

Mickelsen, Olaf, Ph.D. University of Minnesota, Department of Physiological Hygiene, Stadium South Tower, Minneapolis. *Assistant Professor.* (2, 1944)

Mider, George Burroughs, M.D. Univ. of Virginia, School of Medicine, Charlottesville. *Associate Professor of Pathology.* (4, 1940)

Miles, Walter R., A.M., Ph.D. 333 Cedar St., New Haven, Conn. *Professor of Psychology, The School of Medicine and the Institute of Human Relations, Yale University; Member of the National Academy of Sciences.* (1, 1919)

Milhorat, Ade T., M.D. Cornell University Medical College, 1300 York Ave., New York City. *Assistant Professor of Medicine and Instructor in Pharmacology; Research Fellow, Russell Sage Institute of Pathology.* (1, 1934; 3, 1937; 5, 1935)

Miller, Augustus Taylor, Jr., Ph.D.* University of North Carolina Medical School, Chapel Hill. *Associate Professor of Physiology.* (1, 1944)

Miller, Benjamin F., Ch.E., M.D. 9005 Seneca Lane, Bethesda, Md. *Major (Surgeon, R), U. S. Public Health Service. Assistant Professor of Medicine, University of Chicago, Chicago, Ill. (On leave for duration.)* (2, 1938)

Miller, Carey D., M.S. University of Hawaii, Honolulu. *Professor of Food and Nutrition, Hawaii Agricultural Experimental Station.* (5, 1942)

Miller, C. Phillip, M.D., M.S. University of Chicago, Chicago, Ill. *Professor of Medicine.* (4, 1925; 6, 1928)

Miller, Edgar C. L., M.D. %Library, Medical College of Virginia, Richmond. *Directing Librarian.* (6, 1913)

Miller, Edgar G., Jr., Ph.D. 630 W. 168th St., New York City. *Professor of Biological Chemistry, Columbia University.* (2, 1930)

Miller, Franklin R., M.D. Jefferson Medical College and Hospital, Division of Hematology, Philadelphia, Pa. *Associate Professor of Medicine.* (4, 1940)

Miller, Frederick R., A.M., M.D., F.R.C.P. (C), F.R.S. Faculty of Medicine, University of Western Ontario, London, Ont., Canada. *Professor of Physiology.* (1, 1908)

Miller, G. H., A.M., M.D. American University of Beirut, Beirut, Syria. *Dean of the College of Medicine.* (3, 1925)

Miller, Lloyd C., Ph.D. Research and Biologic Laboratory, Winthrop Chemical Co., Rensselaer, N. Y. *Senior Pharmacologist.* (3, 1938)

Miller, R. C., Ph.D. Pennsylvania State College, State College. *Assistant Professor Agricultural and Biological Chemistry.* (5, 1935)

Miller, Zelma Baker, Ph.D., Naval Medical Research Institute, National Naval Medical Center, Bethesda, Md. *Biochemist.* (2, 1940)

Millikan, Glenn A., Ph.D. Johnson Foundation, University of Pennsylvania, Philadelphia. *Fellow in Biophysics.* (1, 1940)

Mills, Clarence A., Ph.D., M.D. Cincinnati General Hospital, Cincinnati, O. *James T. Heady Professor of Experimental Medicine, University of Cincinnati.* (1, 1921; 2, 1921)

Minot, Annie Stone, Ph.D. Vanderbilt University Medical School, Nashville, Tenn. *Research Associate, Department of Pharmacology.* (1, 1923)

Mirsky, Alfred E., Ph.D. The Jewish Hospital, Cincinnati 29, O. (2, 1941)

Mirsky, I. Arthur, M.Sc., M.D., C.M. The Jewish Hospital, Cincinnati, O. *Director, The May Institute for Medical Research; Assistant Professor of Biochemistry, University of Cincinnati.* (1, 1936)

Mitchell, Harold H., M.S. Dept. of Bacteriology, Washington University Medical School, St. Louis, Mo. *Research Fellow.* (6, 1943)

Mitchell, Harold H., M.S., Ph.D. Room 557, Old Agricultural Bldg., University of Illinois, Urbana. *Professor of Animal Nutrition.* (2, 1919; 5, 1933)

Mitchell, Helen S., Ph.D. 699 Forest Rd., New Haven, Conn. (2, 1925; 5, 1933)

Mitchell, Philip H., Ph.D. Brown University Providence 12, R. I. *Robert P. Brown Professor of Biology.* (2, 1909)

Modell, Walter, M.D. Cornell University Medical College, 1300 York Ave., New York, N. Y. *Instructor in Pharmacology.* (3, 1944)

Moe, Gordon Kenneth, Ph.D., M.D. University of Michigan, Ann Arbor. *Assistant Professor of Pharmacology.* (3, 1944)

Molitor, Hans, M.D. 50 Lawrence St., Rahway, N. J. *Director, Merck Institute for Therapeutic Research.* (1, 1933; 3, 1942)

Molomut, Norman, M.A., Ph.D. 200 Walnut St., Yellow Springs, O. *Assistant Bacteriologist, Department of Medicine, Columbia University (on leave); First Lieutenant, Army of U. S. Aero Medical Research.* (6, 1942)

Moon, Virgil H., M.Sc., M.D. Jefferson Medical College, Philadelphia, Pa. *Professor of Pathology.* (4, 1934)

Moore, A. R., Ph.D. University of Oregon, Eugene. *Research Professor of General Physiology in the Department of Psychology.* (1, 1912)

Moore, Carl Vernon, M.D. Washington University School of Medicine, St. Louis, Mo. *Associate Professor of Medicine.* (4, 1938; 5, 1941)

Moore, Lane A., Ph.D. University of Maryland, College Park. *Research Assistant in Dairy Husbandry.* (5, 1940)

Moore, Robert A., M.D. Washington University Medical School, St. Louis, Mo. *Professor of Pathology.* (4, 1929)

Moore, Robert M., M.D. 5808 Westminster, St. Louis, Mo. *Lt. Col., M.C.* (1, 1932)

Moorhouse, Victor Henry K., M.B. University of Manitoba, Winnipeg, Canada. *Professor of Physiology.* (1, 1912)

Morgan, Agnes Fay, M.S., Ph.D. University of California, Berkeley. *Professor of Home Economics; Biochemist, Agric. Exp. Station; Head, Department of Home Economics.* (2, 1929; 5, 1933)

Morgan, Clifford T., M.A., Ph.D.* Harvard University, Cambridge, Mass. *Faculty Instructor in Physiological Psychology.* (1, 1943)

Morgulis, Sergius, A.M., Ph.D. University of Nebraska College of Medicine, Omaha. *Professor of Biochemistry.* (1, 1914; 2, 1916)

Morison, Robert S., M.D. Harvard Medical School, Boston, Mass. *Assistant Professor of Anatomy.* (1, 1938)

Moritz, Alan R., M.D. Harvard Medical School, Boston, Mass. *Professor of Legal Medicine.* (4, 1934)

Morrell, Clarence Allison, M.A., Ph.D. Department of Pensions and National Health, Laboratory of Hygiene, Sussex and John Sts., Ottawa, Canada. *Senior Pharmacologist.* (3, 1937)

Morris, Harold P., M.S., Ph.D. National Cancer Institute, Bethesda, Md. *Senior Nutrition Chemist, U. S. Public Health Service.* (2, 1944; 5, 1943)

Morris, Marion C. Public Health Research Institute of City of New York, Foot of East 15th St., New York City. (6, 1936)

Morrison, Dempsie B., M.S., Ph.D. University of Tennessee College of Medicine, Memphis. *Associate Professor of Chemistry.* (2, 1936)

Morrison, James L., Ph.D. Emory University School of Medicine, Emory University, Ga. *Assistant Professor of Pharmacology.* (3, 1944)

Morse, Minerva, M.S., Ph.D. 5525 Kimbark Ave., Chicago, Ill. *Research Associate, Department of Pediatrics, University of Chicago.* (2, 1934)

Morse, Withrow, Ph.D. 32 Manchester Rd., Eastchester, via Tuckahoe, N. Y. *Consultant.* (2, 1914)

Mortimer, Bernard, Ph.D., M.D. 250 N. Ottawa St., Joliet, Ill. Cook County Hospital, Chicago, Ill. (1, 1936)

Morton, John J., M.D. University of Rochester, School of Medicine and Dentistry, Rochester, N. Y. *Professor of Surgery.* (4, 1927)

Mosenthal, Herman O., M.D. 889 Lexington Ave., New York City. *Professor of Medicine, New York Post-Graduate Medical School.* (2, 1915)

Moulton, C. Robert, Ph.D. 5717 Kenwood Ave., Chicago, Ill. *Editor.* (5, 1933)

Moxon, Alvin L., M.S., Ph.D. College Station, Brookings, S. D. *Chemist, South Dakota Agricultural Experiment Station.* (2, 1944)

Moyer, Carl A., Ph.D.* Seymour Hospital, Eloise, Mich. *Assistant Professor of Surgery.* (1, 1943)

Mudd, Stuart, M.A., M.D. University of Pennsylvania, Philadelphia. *Professor of Bacteriology.* (1, 1921; 4, 1927; 6, 1927)

Muehlberger, Clarence W., M.S., Ph.D. State Health Department Laboratories, Lansing, Mich. *State Toxicologist.* (3, 1928)

Mueller, J. Howard, M.S., Ph.D. 2176 Centre St., N. Roxbury, Mass. *Professor of Bacteriology and Immunology, Harvard Medical School.* (2, 1922; 4, 1927; 6, 1920)

Mukherji, B., M.B., D.Sc. All-India Institute of Hygiene and Public Health, Calcutta. *Director, Biochemical Standardization Laboratory.* (3, 1938)

Mulder, Arthur G., Ph.D. University of Tennessee College of Medicine, Memphis. *Associate Professor of Physiology.* (1, 1937)

Mulinos, M. G., M.D., Ph.D. College of Physicians and Surgeons, Columbia University, 630 W. 168th St., New York City. *Associate Professor of Pharmacology.* (3, 1931)

Mull, James W., Ph.D. Maternity Hospital, 2065 Adelbert Rd., Cleveland, O. *Senior Instructor in Biochemistry in charge of Biochemical Research in Obstetrics, Western Reserve University.* (2, 1937)

Mullin, F. J., M.S., Ph.D. University of Chicago, Chicago, Ill. *Assistant Professor of Physiology.* (1, 1937)

Munsell, Hazel E. 8 N. Main St., Monson, Mass. (5, 1933)

Muntwyler, Edward, Ph.D. Long Island College of Medicine, 350 Henry St., Brooklyn, N. Y. *Professor of Biochemistry.* (2, 1931)

Murlin, John R., A.M., Ph.D., Sc.D. University of Rochester Medical School, 260 Crittenden Blvd., Rochester, N. Y. *Lewis P. Ross Professor Emeritus of Physiology and Director of Department of Vital Economics.* (1, 1906; 2, 1908; 5, 1933)

Murphy, James B., M.D. Rockefeller Institute for Medical Research, 66th St. and York Ave., New York City. *Member.* (4, prior to 1920)

Murray, Everitt G. D., O.B.E., B.A. honors in Natural Science, M.A., L.M.S.S.A., F.R.S.C. McGill University, Montreal, Canada. *Professor of Bacteriology and Immunology and Head of the Department, McGill University; Bacteriologist-in-Chief to the Royal Victoria Hospital, to the Children's Memorial Hospital and to the Alexandra Hospital.* (6, 1933)

Myers, Chester N., Ph.D., Sc.D. 34 Cedar Place, Yonkers 5, N. Y. *Chief, Division Chemotherapy, N. Y. Skin and Cancer Hospital; Associate in Dermatology and Syphilology, College of Physicians and Surgeons; Research Chemist, Vanderbilt Clinic; Director, Chemical and Clinical Research, H. A. Metz Laboratories, Inc.* (2, 1922)

Myers, Victor C., M.A., Ph.D., Sc.D. School of Medicine, Western Reserve University, Cleveland, O. *Professor and Director of Biochemistry.* (1, 1916; 2, 1910; 5, 1933)

Nachmansohn, David, M.D. Dept. of Neurology, College of Physicians and Surgeons, Columbia University, 630 W. 168th St., New York City. *Research Associate in Neurology.* (1, 1940)

Nadler, J. Ernest, M.D., Med. D.Sc. U. S. Navy Recruiting Station, 383 Madison Ave., New York, N. Y. *Instructor in Medicine; Lt. Comdr. (M.C.)* (3, 1940)

Nahum, Louis N., M.D. 1142 Chapel St., New Haven, Conn. *Assistant Professor of Physiology, Yale University.* (1, 1934)

Nash, Thomas P., Jr., M.A., Ph.D. 875 Monroe Ave., Memphis, Tenn. *Professor of Chemistry, College of Medicine; Dean of School of Biological Sciences, University of Tennessee.* (2, 1923)

Nasset, Edmund S., M.S., Ph.D. University of Rochester, 260 Crittenden Blvd., Rochester, N. Y. *Associate Professor of Physiology; Major, San. Corps.* (1, 1932; 5, 1940)

Nathanson, Ira T., M.S., M.D.* Massachusetts General Hospital, Boston. *Instructor in Surgery, Harvard Medical School; Assistant in Surgery, Mass. General Hospital.* (1, 1943)

Nathanson, Morris D., M.D. 658 S. Bonnie Brae St., Los Angeles, Calif. *Associate Clinical Professor of Medicine, University of Southern California School of Medicine.* (3, 1940)

Necheles, Heinrich, M.D., Ph.D. Michael Reese Hospital, Chicago, Ill. *Director, Dept. of Gastro-intestinal Physiology, Michael Reese Hospital; Professorial Lecturer in Physiology, University of Chicago.* (1, 1929)

Neill, James M., Ph.D. Medical College, Cornell University, 1300 York Ave., New York City. *Professor of Bacteriology and Immunology.* (6, 1930)

Neilson, Charles Hugh, A.M., Ph.D., M.D. Humboldt Building, St. Louis, Mo. *Associate Dean and Professor of Medicine, St. Louis University Medical School.* (2, 1906)

Nelson, Arthur A., M.D., Ph.D. Food and Drug Administration, Federal Security Agency, Washington, D. C. *Senior Pathologist, Division of Pharmacology.* (4, 1942)

Nelson, Carl Ferdinand, M.D., Ph.D. Department of Biochemistry, University of Kansas, Lawrence. *Professor of Physiological Chemistry.* (2, 1914)

Nelson, Carl T., A.M., D.M.D., M.D. 4th Service Command Laboratory, Ft. McPherson, Ga. *Captain, M. C., A. U. S.* (6, 1943)

Nelson, Erwin E., Ph.D., M.D. The Burroughs Wellcome and Co., Experimental Research Laboratories, Tuckahoe, N. Y. *Director of Research Laboratories.* (1, 1923; 3, 1924)

Nelson, E. M., M.S., Ph.D. Food and Drug Administration, Federal Security Agency, Washington 25, D. C. *Chief, Vitamin Division.* (2, 1927; 5, 1933)

Nelson, John B., Ph.D. Rockefeller Institute for Medical Research, Princeton, N. J. *Associate Member.* (4, 1934)

Nelson, John M., Ph.D. Columbia University, New York City. *Professor of Organic Chemistry.* (2, 1923)

Nelson, P. Mabel, M.S., Ph.D. Iowa State College, Ames. *Dean, Division of Home Economics.* (5, 1934)

Nelson, Tell, M.A., M.D., 0-263312. Surgeon's Office Headquarters, A.P.O. 958, c/o Postmaster, San Francisco, Calif. *Major, M.C., U.S.A.* (6, 1938)

Nelson, Victor E., M.S. Iowa State College, Ames. *Professor of Physiological Chemistry.* (2, 1924; 5, 1933);

Nelson, Warren O., M.S., Ph.D. Dept. of Anatomy, School of Medicine, Univ. of Iowa, Iowa City. *Professor of Anatomy.* (1, 1937)

Neter, Erwin, M.D. School of Medicine, University of Buffalo, 24 High St., Buffalo, N. Y. *Attending Bacteriologist, Children's Hospital.* (6, 1937)

Nettleship, Anderson, M.D. Indianapolis City Hospitals, Indianapolis. *Pathologist in Chief; Associate Pathologist, University of Indiana Medical School.* (4, 1942)

Neuberg, Carl, Ph.D., M.D. (h.c.), Med. Chem. D. (h.c.), Biol. D. (h.c.), Dr. Eng. (h.c.), LL.D. 905 Westend Ave., New York City. *Research Professor, New York University; Member or hon. member of the Academies of Science of Copenhagen, Göttingen, Leningrad, Lisbon, Lund, Prag, Rome and Upsala.* (2, 1944)

Neumann, Charles, M.D.* Rockefeller Institute for Medical Research, 66th St. and York Ave., New York, N. Y. *Assistant in Medicine and Assistant Resident Physician.* (1, 1944)

Neurath, Hans, Ph.D. School of Medicine, Duke University, Durham, N. C. *Assistant Professor of Biochemistry.* (2, 1940)

Neuwelt, Frank, M.D. 504 Broadway, Gary, Ind. *Research Associate, Department of Gastro-intestinal Research, Michael Reese Hospital.* (1, 1940)

Neuwirth, Isaac, Ph.D. 209 E. 23rd St., New York City. *Associate Professor of Pharmacology and Therapeutics, New York University College of Dentistry.* (2, 1924; 3, 1931)

Newburgh, L. H., M.D. University of Michigan, Ann Arbor. *Professor Clinical Investigation, Medical School.* (5, 1933)

Nice, Leonard B., Ph.D. Chicago Medical School, 710 S. Wolcott Ave., Chicago, Ill. *Professor of Physiology and Pharmacology.* (1, 1921)

Nicholas, John S., M.S., Ph.D. Osborn Zoological Laboratory, Yale University, New Haven, Conn. *Bronson Professor of Comparative Anatomy.* (1, 1927)

Nicholson, Hayden C., M.S., M.D. University of Michigan, Ann Arbor. *Associate Professor of Physiology. Major, Office of the Air Surgeon, Hq. Army Air Forces, Washington 25, D. C.* (1, 1932)

Nicolet, Ben H., Ph.D. Bureau of Dairy Industry, U. S. Department of Agriculture, Beltsville, Md. *Senior Chemist.* (2, 1932)

Niemann, Carl G., Ph.D. California Institute of Technology, Pasadena 4, Calif. *Associate Professor, Organic Chemistry.* (2, 1940)

Nigg, Clara, M.A., Ph.D. c/o E. R. Squibb & Sons, New Brunswick, N. J. (6, 1929)

Nims, Leslie F., M.A., Ph.D. Yale University School of Medicine, 333 Cedar St., New Haven, Conn. *Assistant Professor of Physiology.* (1, 1940)

Noble, Robert Laing, M.D., Ph.D. Research Institute of Endocrinology, McGill University, Montreal, Canada. *Research Assistant.* (1, 1941)

Nord, F. F., Ph.D. Fordham University, Dept. of Organic Chemistry, New York City. *Professor of Chemistry.* (2, 1940)

Norris, Earl R., Ph.D. University of Washington, Seattle. *Professor of Chemistry.* (2, 1938)

Norris, L. C., Ph.D. Rice Hall, Cornell University, Ithaca, N. Y. *Professor of Nutrition; Secretary, School of Nutrition.* (2, 1939; 5, 1934)

Northrop, J. H., M.A., Ph.D., Sc.D., LL.D. Rockefeller Institute for Medical Research, Princeton, N. J. *Member.* (2, 1938)

Northup, David W., M.A., Ph.D. West Virginia University Medical School, Morgantown. *Associate Professor of Physiology.* (1, 1936)

Novy, F. G., M.D., Sc.D., LL.D. 721 Forest Ave., Ann Arbor, Mich. *Dean Emeritus of the Medical School and Professor Emeritus of Bacteriology, University of Michigan; Member, National Academy of Sciences.* (2, 1906)

Nye, Robert N., M.D. Boston City Hospital, Boston, Mass. *Editor, New England Journal of Medicine.* (6, 1923)

Oberst, Fred W., M.S., Ph.D. The Wm. S. Merrell Co., Lockland Station, Cincinnati, O. *Chief, Division of Biochemistry.* (2, 1936)

Ochoa, Severo, M.D. New York University College of Medicine, New York City. *Research Associate in Medicine.* (2, 1942)

Ogden, Eric, M.R.C.S. (England), L.R.C.P. (London). University of California, Berkeley. *Assistant Professor of Physiology.* (1, 1941)

O'Hare, James P., M.D. 520 Commonwealth Ave., Boston, Mass. *Physician, Peter Bent Brigham Hospital; Assistant Professor of Medicine, Harvard Medical School.* (4, 1927)

Okey, Ruth, Ph.D. 1583 Life Sciences Bldg., University of California, Berkeley. *Professor of Home Economics and Biochemist, State Exp. Station.* (2, 1922; 5, 1933)

Olcott, Harold S., M.S., Ph.D. Western Regional Research Laboratory, U. S. Department of Agriculture, Albany 6, Calif. *Senior Chemist.* (2, 1935)

Olitsky, Peter K., M.D. Rockefeller Institute for Medical Research, 66th St. and York Ave., New York City. *Member.* (4, 1923; 6, 1917)

Oliver, Jean Redman, M.D. Hoagland Laboratory, 335 Henry St., Brooklyn, N. Y. *Professor of Pathology, Long Island College of Medicine.* (1, 1924; 4, 1924)

Oliver, Wade W., M.D. Hoagland Laboratory, 335 Henry St., Brooklyn, N. Y. *Professor of Bacteriology, Long Island College of Medicine.* (4, 1925)

Olmsted, J. M. D., M.A., Ph.D. University of California, Berkeley. *Professor of Physiology.* (1, 1920)

Olson, Carl, Jr., D.V.M., Ph.D. Massachusetts State College, Amherst. *Research Professor of Veterinary Science.* (4, 1937)

Opie, Eugene L., M.D., Sc.D., LL.D. Rockefeller Institute for Medical Research, 66th St. and York Ave., New York 21, N. Y. *Member, National Academy of Sciences.* (1, 1906; 4, 1913; 6, 1923)

Oppenheimer, Enid Tribe. 124 E. 61st St., New York City. *Instructor in Physiology, Columbia University.* (1, 1932)

Oppenheimer, Ernst, M.D. Ciba Pharmaceutical Products, Inc., Lafayette Park, Summit, N. J. *Vice-President in charge of Medical Research.* (3, 1944)

Oppenheimer, Morton Joseph, Ed.M., M.D. 3400 N. Broad St., Philadelphia, Pa. *Associate Professor of Physiology, Temple University School of Medicine.* (1, 1942)

Orent-Keiles, Elsa, D.Sc. Bureau of Human Nutrition and Home Economics, U. S. Department of Agriculture, Beltsville, Md. *In Charge of Nutrition Investigations; Assistant Chief, Foods and Nutrition Division.* (2, 1935; 5, 1935)

Ort, John M., Ph.D. 356 Raymond St., Rockville Centre, Long Island, N. Y.; American Pharmaceutical Company, New York City. *Director of Laboratories.* (2, 1932)

Orten, James M., M.S., Ph.D. Wayne University College of Medicine, Detroit, Mich. *Associate Professor of Physiological Chemistry.* (2, 1936; 5, 1937)

Orth, O. Sidney, M.S., Ph.D., M.D. University of Wisconsin Medical School, Madison. *Assistant Professor of Pharmacology.* (1, 1942; 3, 1944)

Osborne, Stafford L., B.P.E., M.S., Ph.D. Northwestern University Medical School, 303 E. Chicago Ave., Chicago, Ill. *Assistant Professor of Physical Therapy.* (1, 1941)

Oster, Robert H., Ph.D. University of Maryland Medical School, Greene and Lombard Sts., Baltimore. *Assistant Professor of Physiology.* (1, 1938)

Osterberg, Arnold E., M.S., Ph.D. Mayo Clinic, Rochester, Minn. *Head, Clinical Biochemistry; Associate Professor, Mayo Foundation.* (2, 1933)

Osterhout, Marian I.* Rockefeller Institute for Medical Research, 66th St. and York Ave., New York City 21. (1, 1944)

Osterhout, W. J. V., Ph.D. Rockefeller Institute, 66th St. and York Ave., New York City. *Member Emeritus of the Institute; Member of the National Academy of Sciences.* (1, 1910)

Owen, Seward E., M.S., Ph.D. 418 So. 20th Ave., Maywood, Ill. *Major, S. E. Sn. Corps.* (1, 1938)

Pace, Donald M., Ph.D.* Dept. of Physiology and Pharmacology, College of Pharmacy, University of Nebraska, Lincoln. *Associate Professor of Physiology.* (1, 1944)

Pack, George T., M.D. 139 E. 36th St., New York City 16. *Fellow in Cancer Research, Memorial Hospital.* (1, 1924)

Packchanian, Ardzroony, Ph.D. School of Medicine, University of Texas, Galveston. *Associate Pro-*

fessor of Bacteriology and Tropical Medicine. (6, 1943)

Page, Irvine H., M.D. Indianapolis City Hospital, Indianapolis, Ind. *Director of Clinical Research.* (1, 1937; 2, 1932)

Painter, Elizabeth E., Ph.D. College of Physicians and Surgeons, Columbia University, 630 W. 168th St., New York. *Instructor in Physiology.* (1, 1941)

Palmer, Albert H., Ph.D. Pennsylvania State College School of Agriculture, State College. *Assistant Professor of Biochemistry.* (2, 1934)

P'An, S. Y., M.D. Peiping Union Medical College, Peiping, China. *Assistant in Pharmacology.* (3, 1941)

Pangborn, Mary C., Ph.D. 20 Morris St., Albany, N. Y. *Assistant Biochemist, New York State Department of Health, Division of Laboratories and Research.* (2, 1941)

Pappenheimer, Alwin M., Jr., Ph.D. 19th Medical General Laboratory, APO 5467, c/o Postmaster, San Francisco, Calif. *Major, Sn.C., AUS.* (2, 1941; 6, 1938)

Pappenheimer, Alwin M., M.D. 630 W. 168th St., New York City. *Professor of Pathology, Columbia University.* (4, 1922)

Park, Edwards A., M.D. Johns Hopkins Hospital, Baltimore, Md. *Professor of Pediatrics, Johns Hopkins University.* (4, 1923)

Parker, George Howard, Sc.D. 16 Berkeley St., Cambridge, Mass. *Professor of Zoology Emeritus, Harvard University; Member of the National Academy of Sciences.* (1, 1900)

Parker, Robert F., M.D. Lakeside Hospital, 2065 Adelbert Rd., Cleveland, O. *Associate Professor of Medicine.* (4, 1942; 6, 1935)

Parkins, William M., M.A., Ph.D. School of Medicine, University of Pennsylvania, Philadelphia. *Research Associate, Harrison Department of Surgical Research.* (1, 1939)

Parpart, Arthur K., Ph.D. Guyot Hall, Princeton University, Princeton, N. J. *Associate Professor of Physiology.* (1, 1937)

Parr, Leland W., Ph.D. The George Washington University School of Medicine, 1335 H St., N.W. Washington, D. C. *Professor of Bacteriology.* (4, 1940)

Parsons, Helen T., M.S., Ph.D. University of Wisconsin, Madison. *Professor of Home Economics; In Charge of Purnell Research in Nutrition.* (2, 1929; 5, 1933)

Parsons, Robert J., M.D. University of Michigan, Ann Arbor. *Assistant Professor of Pathology.* (4, 1939)

Paschkis, Karl E., M.D. 1025 Walnut St., Philadelphia, Pa. *J. Ewing Mears Fellow in Physiology and Medicine, Jefferson Medical College; Chief Clinical Assistant, Endocrine Clinic, Jefferson Medical College Hospital.* (1, 1942)

Patterson, Thos. L., A.M., M.S., Ph.D. Wayne University College of Medicine, 1512 St. Antoine St., Detroit, Mich. *Research Professor of Physiology.* (1, 1920)

Paul, John R., M.D., A.M. 330 Cedar St., New Haven, Conn. *Professor of Preventive Medicine, Yale University Medical School.* (4, 1927; 6, 1937)

Pearce, John Musser, M.D. Long Island College of Medicine, Hoagland Laboratory, 335 Henry St., Brooklyn, N. Y. *Associate Professor of Pathology.* (4, 1942)

Pearce, Louise, M.D. Rockefeller Institute for Medical Research, Princeton, N. J. *Associate Member in Pathology and Bacteriology.* (3, 1915; 4, 1925)

Pearcy, Frank, Ph.D., M.D. 471 Park Ave., New York City. (1, 1928)

Pearse, Herman E., M.D. School of Medicine and Dentistry, University of Rochester, Crittenden Blvd., Rochester, N. Y. *Associate Professor of Surgery.* (4, 1932)

Pearson, Paul B., Ph.D. A & M College of Texas, College Station. *Professor of Nutrition; Nutritionist, Agricultural Experiment Station.* (2, 1944; 5, 1940)

Pease, Marshall C., Jr., M.D. 155 E. 62nd St., New York City. *Clinical Professor of Pediatrics, New York Post-Graduate Medical School and Hospital, Columbia University.* (6, 1920)

Pemberton, Ralph, M.S., M.D. University of Pennsylvania, Philadelphia. *Professor of Medicine, Graduate School of Medicine.* (5, 1933)

Penfield, Wilder G., M.D., D.Sc. McGill University, Montreal, Que., Canada. *Professor of Neurology and Neurosurgery.* (1, 1932)

Pennington, Mary Engle, Ph.D. 233 Broadway, New York 7, N. Y. *Consultant in Connection with the Handling, Transportation and Storage of Perishables.* (2, 1908)

Peoples, S. Anderson, M.D. Baylor University College of Medicine, Houston, Texas. *Professor of Pharmacology.* (3, 1937)

Perlzweig, William A., A.M., Ph.D. Box 3711, Duke Hospital, Durham, N. C. *Professor of Biochemistry, Duke University; Biochemist, Duke Hospital.* (2, 1924; 5, 1944)

Permar, Howard H., M.D. Pathologic Laboratories, Mercy Hospital, Pittsburgh, Pa. *Director of Laboratories.* (4, 1925)

Peters, John P., M.D. 123 Marvel Road, New Haven 15, Conn. *Sterling Professor of Medicine, Yale University.* (2, 1922)

Petersen, William F., M.D. 1322 Astor St., Chicago, Ill. *Professor of Pathology, University of Illinois.* (3, 1923; 4, 1923)

Peterson, William H., A.M., Ph.D. Biochemistry Building, University of Wisconsin, Madison. *Professor of Biochemistry.* (2, 1919; 5, 1936)

Petroff, S. A., Ph.D., Sc.D. Sea View Hospital, West New Brighton, Staten Island, N. Y. *Director of Bacteriology and Immunology.* (6, 1926)

Pett, L. B., M.D., Ph.D. Department of National Health and Welfare, Ottawa, Canada. *Director of Nutrition.* (2, 1937)

Peugnet, Hubert B., M.D. 4530 McPherson, St. Louis, Mo. *Major, M.C.* (1, 1938)

Pfeiffer, Carl C., Ph.D., M.D. Naval Medical Research Institute, Bethesda, Md. *Lieutenant, M.C., U.S.N.R.* (3, 1938)

Pfiffner, Joseph J., Ph.D. Research Laboratories, Parke, Davis & Co., Detroit 32, Mich. *Research Chemist.* (1, 1931; 2, 1931)

Phatak, Nilkanth M., M.S., Ph.D. North Pacific College of Oregon, School of Dentistry, Portland. *Associate Professor of Physiology, Pharmacology, and Research; and Instructor, Dept. of Pharmacology, University of Oregon Medical School, Portland. Captain, Sn. C.* (3, 1941)

Phillips, Paul H., Ph.D. University of Wisconsin, Madison. *Professor of Biochemistry.* (2, 1940; 5, 1938)

Phillips, Robert Allan, M.D. Rockefeller Institute for Medical Research, New York City. *Fellow.* (1, 1938)

Pick, Ernst Peter, M.D. 19 E. 98th St., New York City. *Associate Pharmacologist to the Mt. Sinai Hospital; Clinical Professor of Pharmacology in Columbia University.* (3, 1940)

Pierce, Harold B., M.S., Ph.D. College of Medicine, University of Vermont, Burlington. *Professor and Head of Physiological Chemistry.* (2, 1929; 5, 1933)

Pierce, Harold Fisher, Ph.D., M.D. Old Farms Convalescent Hospital, Avon, Conn. *Major, MC; Surgeon, Old Farms Hospital, ASF.* (1, 1928)

Pierce, Ira H., M.S., Ph.D. Univ. of Iowa, Iowa City. *Associate Professor of Pharmacology.* (3, 1933)

Pike, Frank H., Ph.D. 630 W. 168th St., New York City. *Associate Professor of Physiology, Columbia University.* (1, 1907)

Pilcher, J. Douglas, M.D. City Hospital, Scranton Road, Cleveland, O. *Associate Professor of Pediatrics, Western Reserve Medical School.* (1, 1912; 3, 1911)

Pillemer, Louis, Ph.D. The Gilliland Laboratories, Inc., Marietta, Pa. (6, 1942)

Pincus, Gregory, M.S., Sc.D. Clark University, Worcester, Mass. *Visiting Professor of Experimental Zoology.* (1, 1935)

Pinkerton, Henry, M.D. St. Louis University School of Medicine, St. Louis, Mo. *Professor of Pathology.* (4, 1931)

Pinkston, James O., Ph.D. 6627 Heartwood Dr., Oakland, Calif. *Professor of Pharmacology, School of Medicine, American University of Beirut.* (1, 1936; 3, 1939)

Pinson, Ernest A., Ph.D.* Biophysics Branch, Aeromedical Laboratory, Wright Field, Dayton, O. *Major, Air Corps.* (1, 1943)

Pittman, Martha S., A.M., Ph.D. Kansas State College, Manhattan. *Head of Department of Food Economics and Nutrition.* (5, 1933)

Pitts, Robert F., Ph.D., M.D. Cornell Medical Center, 1300 York Ave., New York City. *Associate Professor of Physiology.* (1, 1934)

Plass, Everett D., M.D. University Hospital, Iowa City, Iowa. *Professor and Head of Department of Obstetrics and Gynecology, State University of Iowa.* (2, 1922)

Plotz, Harry, M.D. Army Medical Center, Army Medical School, Washington, D. C. *Colonel, Chief of the Division of Virus and Rickettsial Diseases; Chief of Service, Pasteur Institute, Paris, France.* (6, 1917)

Pohlman, Augustus G., M.D. 4056 Farmouth Dr., Los Angeles, Calif. *Associate Clinical Professor, Department of Otolaryngology, University of Southern California School of Medicine.* (1, 1934)

Pollack, Herbert, Ph.D., M.D. 598 Madison Ave., New York City 22. *Associate in Medicine and Physician in Charge of Metabolism Clinics, Mt. Sinai Hospital.* (1, 1933; 5, 1935)

Pomerat, Charles Marc, Ph.D.* University of Texas Medical School, Galveston. *Professor of Anatomy.* (1, 1944)

Pond, Samuel E., A.M., Ph.D. 400 S. Main St., East Hartford, Conn. *Consulting Engineer, P. and W. A. Division, United Aircraft Corp.* (1, 1924)

Ponder, Eric, M.D., Sc.D. The Nassau Hospital, Mineola, Long Island, N. Y. (1, 1931)

Popper, Hans, Ph.D., M.D. University of Illinois College of Medicine, 1825 W. Harrison St., Chicago. *Director of Laboratories and of the Hektoen Institute for Medical Research of Cook County Hospital.* (4, 1942)

Porter, Eugene L., A.M., Ph.D. University of Texas, Medical Branch, Galveston. *Professor of Physiology.* (1, 1913)

Porter, Thelma, University of Chicago, Chicago, Ill. *Prof. and Head of Department of Home Economics.* (5, 1944)

Porter, William Townsend, M.D., Sc.D., LL.D. Dover, Mass. *Professor Emeritus of Comparative Physiology, Harvard University.* (1, 1891)

Potter, Truman S., M.D. Dartmouth Medical School, Hanover, N. H. (6, 1939)

Potter, Van Rensselaer, M.S., Ph.D. McArdle Memorial Laboratory, University of Wisconsin Medical School, Madison. *Assistant Professor of Oncology.* (2, 1941)

ovitzky, Olga R., M.D., D.P.H. 235 E. 22nd St., New York City. *Bacteriologist, Bureau of Laboratories, New York City Department of Health.* (6, 1920)

owell, Horace M., Sc.D. 5565 Washington Blvd., Indianapolis, Ind. *Bacteriologist, Eli Lilly & Co.* (6, 1934)

ower, Marschelle H., M.S., Ph.D. Mayo Clinic, Rochester, Minn. *Associate Professor of Physiological Chemistry, Mayo Foundation, University of Minnesota.* (2, 1932)

ratt, Frederick H., A.M., M.D. Wellesley Hills 82, Mass. *Professor of Physiology, Emeritus, Boston University School of Medicine.* (1, 1919)

ratt, Joseph H., A.M., M.D. Sc.D. New England Medical Center, 25 Bennet St., Boston, Mass. *Physician-in-Chief, Boston Dispensary, and Joseph H. Pratt Diagnostic Clinic; Professor of Clinical Medicine, Tufts Medical School.* (1, 1910; 3, 1910; 4, 1927)

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rosser, C. Ladd, Ph.D. University of Illinois, Urbana. *Associate Professor of Physiological Zoology.* (1, 1935)

ucher, George W., Ph.D. Connecticut Agricultural Experiment Station, New Haven. *Research Associate.* (2, 1927)

uestow, Charles B., M.D., M.S., Ph.D. University of Illinois, College of Medicine, 1853 W. Polk St., Chicago. *Assistant Professor of Surgery. Lt. Col. (MC) AUS.* (1, 1934)

ugsley, Leonard I., Ph.D. Department of Pensions and National Health, Laboratory of Hygiene, Ottawa, Canada. *Pharmacologist.* (2, 1937)

ueen, Frank B., M.D. Passavant Memorial Hospital, Chicago, Ill. *Assistant Professor of Pathology, Northwestern University Medical School; Assistant Director, Patterson Cancer Clinic of Northwestern University Medical School, and Director, Patterson Laboratory for Cancer Research, Passavant Memorial Hospital; Director of Laboratories, Passavant Memorial Hospital.* (4, 1941)

uick, Armand J., M.D., Ph.D. 561 N. 15th St., Milwaukee, Wis. *Associate Professor of Pharmacology, Marquette Medical School.* (2, 1932; 3, 1937)

Quigley, J. P., Ph.D. Western Reserve University, Cleveland, O. *Professor of Gastro-Intestinal Physiology.* (1, 1929)

Quinby, William Carter, M.D. Peter Bent Brigham Hospital, Boston, Mass. *Clinical Professor of Genito-urinary Surgery, Harvard Medical School.* (1, 1916)

Quinn, Edmond John, Ph.D. 106 N. Lee Ave., Rockville Center, Long Island, N. Y. *Medicinal Sales Division, Merck & Co., Inc., Rahway, N. J.* (2, 1927; 5, 1933)

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Rackemann, Francis M., M.D. 263 Beacon St., Boston, Mass. *Physician, Massachusetts General Hospital; Lecturer in Medicine, Harvard Medical School.* (6, 1923)

Raffel, Sidney, Sc.D., M.D. Department of Bacteriology and Experimental Pathology, Stanford University, Calif. *Assistant Professor.* (6, 1938)

Rahn, Hermann, Ph.D.* University of Rochester School of Medicine and Dentistry, Rochester, N. Y. *Instructor in Physiology.* (1, 1944)

Raiziss, George W., Ph.D. 1720 Lombard St., Philadelphia, Pa. *Professor of Chemotherapy, Graduate School of Medicine, and Director, Dermatological Research Laboratory, University of Pennsylvania.* (2, 1913)

Rake, Geoffrey W., M.B., M.R.C.S., L.R.C.P. Division of Microbiology, The Squibb Institute for Medical Research, New Brunswick, N. J. *Head, Division of Microbiology.* (6, 1939)

Rakestraw, Norris W., A.M., Ph.D. Brown University, Providence, R. I. *Professor of Chemistry.* (2, 1925)

Rakieten, Nathan, Ph.D. Cheplin Biological Laboratories, Syracuse, N. Y. *Penicillin Unit.* (1, 1941)

Ralli, Elaine P., M.D. 477 First Ave., New York City. *Associate Professor of Medicine, New York University College of Medicine.* (1, 1934; 5, 1933)

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Rammelkamp, Charles H., M.D. Commission on Acute Respiratory Diseases, Station Hospital, Section 2, Fort Bragg, N. C. *Instructor of Medicine, Boston University Medical School (on leave); Consultant to the Secretary of War.* (6, 1943)

Ramsey, Robert Weberg, M.S., Ph.D. Medical College of Virginia, Richmond. *Associate Professor of Physiology and Pharmacology.* (1, 1939)

Randall, Lowell O., Ph.D. Burroughs Wellcome Co., Tuckahoe, N. Y. *Pharmacologist.* (2, 1939)

Randall, Walter C., M.S., Ph.D.* St. Louis University, School of Medicine, 1402 S. Grand Blvd., St. Louis, Mo. *Instructor in Physiology.* (1, 1943)

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Rapport, David, M.D. 416 Huntington Ave., Boston, Mass. *Professor of Physiology, Tufts College Medical School.* (1, 1922)

Rasmussen, Andrew Theodore, Ph.D. University of Minnesota Medical School, Minneapolis. *Professor of Neurology.* (1, 1919)

Ratner, Bret, M.D. New York University College of Medicine, 50 E. 78th St., New York City. *Professor of Pediatrics.* (4, 1940; 6, 1928)

Ratner, Sarah, Ph.D. Dept. of Medicine, College of Physicians and Surgeons, Columbia University, 630 W. 168th St., New York City. *Associate in Biochemistry.* (2, 1944)

Raulston, B. O., M.D. 200 S. Hudson Ave., Los Angeles, Calif. *Professor of Medicine, Director of Clinical Teaching, and Associate Dean, the University of Southern California, School of Medicine.* (3, 1942)

Ravdin, I. S., M.D. University of Pennsylvania School of Medicine, Philadelphia. *Harrison Professor of Surgery; Surgeon, Hospital of the University of Pennsylvania.* (1, 1930; 4, 1930)

Ray, George B., A.M., Ph.D. Long Island College of Medicine, 350 Henry St., Brooklyn, N. Y. *Professor of Physiology and Pharmacology.* (1, 1924)

Raymond, Albert L., Ph.D. G. D. Searle & Co., P. O. Box 5110, Chicago 80, Ill. *Director of Research.* (2, 1932)

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Redfield, Alfred C., Ph.D. Woods Hole, Mass. *Professor of Physiology, Harvard University.* (1, 1919)

Reed, Carlos Isaac, A.M., Ph.D. College of Medicine, University of Illinois, 1853 W. Polk St., Chicago. *Professor of Physiology.* (1, 1923)

Reed, Howard S., Ph.D. 3048 Life Sciences Bldg., University of California, Berkeley. *Professor of Plant Physiology.* (2, 1909)

Rees, Maurice Holmes, A.M., Ph.D., M.D. University of Colorado School of Medicine, Denver. *Professor of Physiology and Pharmacology; Dean of the University of Colorado School of Medicine and Hospitals.* (1, 1922)

Reid, Marion Adelaide, A.M., Ph.D. 80 E. Concord St., Boston, Mass. *Instructor in Physiology, Boston University.* (1, 1941)

Reimann, Hobart A., M.D. Jefferson Hospital, Philadelphia, Pa. *Professor of Medicine, Jefferson Medical College.* (4, 1933)

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Reiner, Laszlo, M.D., Ph.D. 165 Franklin St., Bloomfield, N. J. *Research Department, Wallace & Tiernan Company.* (2, 1942; 6, 1933)

Reinhold, John G., M.S., Ph.D. Philadelphia General Hospital, 34th St. and Curie Ave., Philadelphia, Pa. *Chief Biochemist; Instructor in Physiological Chemistry, University of Pennsylvania.* (2, 1936)

Remington, John W., M.S., Ph.D.* University of Georgia, School of Medicine, Augusta. *Assistant Professor of Physiology.* (1, 1943)

Remington, Roe E., M.A., Ph.D., D.Sc. 69 Atlantic Coastal Highway, Charleston, S. C. *Consultant.* (2, 1930; 5, 1934)

Renfrew, Alice G., Ph.D. Mellon Institute of Industrial Research, University of Pittsburgh, Pittsburgh, Pa. *Fellow, Department of Research in Pure Chemistry.* (2, 1939)

Renshaw, Birdsey, M.A., Ph.D. Oberlin College, Oberlin, O. *Assistant Professor of Physiology.* (1, 1941)

Reynolds, Chapman, M.D. Louisiana State University, School of Medicine, New Orleans. *Assistant Professor of Pharmacology.* (3, 1937)

Reynolds, Samuel R. M., Ph.D. School of Aviation Medicine, Randolph Field, Texas. *Captain, A.U.S. Research Associate, Department of Embryology, Carnegie Institution of Washington.* (1, 1932)

Reznikoff, Paul, M.D. New York Hospital, 525 E. 68th St., New York City. *Associate Professor of Clinical Medicine, Cornell University Medical College.* (1, 1927)

Rhoads, Cornelius Packard, M.D. Memorial Hospital, 444 E. 68th St., New York City. *Director.* (4, 1930)

Rice, Christine E., M.A., Ph.D. Department of Bacteriology, Queen's University, Kingston, Ontario, Canada. (6, 1938)

Rice, James C., A.M., Ph.D. University of Mississippi, P. O. Box 475, University. *Professor of Pharmacology.* (3, 1941)

Rich, Arnold Rice, M.D. Johns Hopkins Hospital, Baltimore, Md. *Associate Professor of Pathology, Johns Hopkins University.* (4, 1924)

Richards, Alfred N., A.M., Ph.D., Sc.D., M.D. (hon.), LL.D. University of Pennsylvania Medical School, Philadelphia. *Professor of Pharmacology and Vice-President in Charge of Medical Affairs; Member, National Academy of Sciences.* (1, 1900; 2, 1906; 3, 1909)

Richards, Oscar W., M.A., Ph.D. Research Department, Spencer Lens Co., 19 Doat St., Buffalo, N. Y. *Research Biologist.* (1, 1934)

Richards, Richard Kohn, M.D. Abbott Laboratories, North Chicago, Ill. *Director, Pharmacologic Research.* (1, 1938)

Richardson, Arthur P., M.D. Squibb Institute for Medical Research, New Brunswick, N. J. *Head, Division of Pharmacology.* (3, 1939)

Richardson, Luther R., Ph.D. University of Missouri, Columbia. *Instructor in Agricultural Chemistry.* (5, 1942)

Richter, Curt P., Ph.D. Phipps Psychiatric Clinic, The Johns Hopkins Hospital, Baltimore, Md. *Associate Professor of Psycho-biology, Johns Hopkins University.* (1, 1924)

Richter, Maurice N., M.D. 303 E. 20th St., New York City. *Professor of Pathology, Columbia University, New York Post-Graduate Medical School; Director, Department of Pathology, New York Post-Graduate Medical School and Hospital.* (4, 1931)

Ricketts, Henry T., M.D. Dept. of Medicine, University of Chicago, Chicago, Ill. *Associate Professor of Medicine.* (1, 1940)

Riddle, Oscar, Ph.D. Cold Spring Harbor, L. I., N. Y. *Resident Staff, Carnegie Station for Experimental Evolution; Member of the National Academy of Sciences.* (1, 1919)

Riegel, Byron, A.M., Ph.D. Department of Chemistry, Northwestern University, Evanston, Ill. *Associate Professor.* (2, 1942)

Riegel, Cecilia, M.S., Ph.D. Room 563, University Hospital, Philadelphia, Pa. *Research Associate, Department of Research Surgery, University of Pennsylvania School of Medicine.* (2, 1938)

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Rinehart, James F., M.D. University of California Medical School, Parnassus and Third Aves., San Francisco. *Professor of Pathology and Medicine.* (4, 1933)

Ring, Gordon C., M.A., Ph.D. Box 616, Tombstone, Ariz. *Captain, Medical Corps.* (1, 1933)

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Rittenberg, David, Ph.D. 630 W. 168th St., New York City. *Assistant Professor, College of Physicians and Surgeons, Columbia University.* (2, 1939)

Ritzman, E. G., A.M., Science (hon.). University of New Hampshire, Durham. *Research Professor.* (5, 1933)

Rivers, T. M., M.D., Sc.D. The Hospital of the Rockefeller Institute for Medical Research, 66th St. and York Ave., New York City. *Director of the Hospital; Member of the National Academy of Sciences.* (4, 1925; 6, 1921)

Robb, Jane Sands, Sc.D., M.D. College of Medicine, Syracuse University, 761 Irving Ave., Syracuse, N. Y. *Associate Professor of Pharmacology.* (1, 1924)

Robbins, Benjamin Howard, M.S., M.D. Vanderbilt Univ. School of Medicine, Nashville, Tenn. *Associate Professor of Pharmacology.* (3, 1936)

Roberts, Edward F., M.D., Ph.D. Fourth Service Command, Medical Laboratory, Fort McPherson, Ga. (6, 1932)

Roberts, Lydia J., Ph.D. University of Chicago, Chicago, Ill. *Professor and Chairman of Department of Home Economics.* (5, 1933)

Robertson, Elizabeth Chant, M.D., M.A., Ph.D. University of Toronto, Toronto, Canada. *Research Fellow in Paediatrics.* (5, 1939)

Robertson, Oswald H., M.D. University of Chicago, Chicago, Ill. *Professor of Medicine.* (4, 1932)

Robinson, Charles Summers, Ph.D. Medical School, Vanderbilt University, Nashville, Tenn. *Professor of Biochemistry.* (2, 1925)

Robinson, Elliott S., M.D., Ph.D. 3034 S. Buchanan St., Arlington, Va. *Lt. Col., M.C.* (6, 1935)

Robinson, G. Canby, M.D., Sc.D., LL.D. Johns Hopkins Hospital, Baltimore, Md. *Lecturer in Medicine, Johns Hopkins University.* (1, 1912; 3, 1921)

Robinson, George Henry, Ph.D. 320 E. North Ave., N. S., Pittsburgh, Pa. *Bacteriologist, Wm. H. Singer Research Laboratory and Allegheny General Hospital; Lecturer in Bacteriology,*

University of Pittsburgh School of Medicine. (4, 1930)

Robinson, Howard W., M.S., Ph.D. Broad and Ontario Sts., Philadelphia, Pa. *Professor of Physiological Chemistry, Temple University School of Medicine.* (2, 1929)

Robinson, Sid, Ph.D. Indiana University Medical School, Bloomington. *Associate Professor of Physiology.* (1, 1941)

Robscheit-Robbins, F. S., Ph.D. University of Rochester School of Medicine and Dentistry, Rochester, N. Y. *Associate in Pathology.* (1, 1925; 4, 1930)

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Roeder, Kenneth D., M.A. Tufts College, Medford, Mass. *Associate Professor of Biology.* (1, 1942)

Roepke, Martin Henry, Ph.D. University Farm, St. Paul, Minn. *Professor, Veterinary Medicine.* (3, 1937)

Rogers, Charles G., A.M., Ph.D., Sc.D. Oberlin College, Oberlin, O. *Professor of Comparative Physiology.* (1, 1911)

Rogers, Fred T., A.M., Ph.D., M.D. Dallas Medical and Surgical Clinic, 4540 Bordeaux Ave., Dallas, Texas. (1, 1917)

Rogoff, Julius M., Ph.G., M.D., Sc.D. School of Medicine, University of Pittsburgh, Pittsburgh, Pa. *Professor of Endocrinology.* (1, 1916; 3, 1916)

Ronzoni, Ethel, M.A., Ph.D. Washington University Medical School, St. Louis 4, Mo. *Assistant Professor of Biological Chemistry.* (2, 1923)

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Root, Walter S., Ph.D. College of Physicians and Surgeons, Columbia University, 630 W. 168th St., New York City. *Associate Professor of Physiology.* (1, 1932)

Rosahn, Paul D., M.D. 92 Grand St., New Britain, Conn. *Pathologist, New Britain General Hospital; Assistant Clinical Professor of Pathology, Yale University School of Medicine, New Haven.* (4, 1934)

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Rose, William C., Ph.D. University of Illinois, Urbana. *Professor of Biochemistry and Acting Head of the Chemistry Department; Member National Academy of Sciences.* (2, 1912; 5, 1933)

Rosenblueth, Arturo, M.D. Instituto Nacional de Cardiologia, Mexico D.F., Mexico. (1, 1932)

Rosenfeld, Morris, M.D. Johns Hopkins School of Medicine, Baltimore, Md. *Associate in Pharmacology and Experimental Therapeutics. Captain, M.C.* (3, 1934)

Rosenow, Edward C., M.D., hon. LL.D. and D.Sc. California Institute of Technology, Pasadena 9. (4, 1913; 6, 1915)

Rosenthal, Sanford M., M.D. National Institute of Health, Washington, D. C. *Senior Pharmacologist, U. S. Public Health Service.* (3, 1925)

Rosenthal, S. R., M.D., Ph.D. University of Illinois College of Medicine, Chicago. *Assistant Professor of Bacteriology and Public Health in Dept. of Pathology and Bacteriology; Director, Tice Laboratory for B. C. G. Vaccination against Tuberculosis, Municipal Tuberculosis Sanatorium.* (4, 1941)

Ross, Joseph F., M.D. The Robert Dawson Evans Memorial, 65 E. Newton St., Boston, Mass. *Member of the Department; Physician, Massachusetts Memorial Hospital; Assistant Professor of Medicine, Boston University School of Medicine; Welch Fellow of Internal Medicine of the Division of Medical Sciences of the National Research Council.* (4, 1941)

Ross, William F., Ph.D. Shell Oil Company, 100 Bush St., San Francisco, Calif. *Chief Research Chemist.* (2, 1940)

Roth, George B., M.D. 1335 H St., N.W., Washington, D. C. *Professor of Physiology and Pharmacology, George Washington University School of Medicine.* (1, 1914; 3, 1911)

Roth, Grace M., M.S., Ph.D. Mayo Clinic, Rochester, Minn. *Associate in Clinical Physiology.* (1, 1939)

Roth, Paul, M.D. Battle Creek Sanitarium, Battle Creek, Mich. *Director of Physical Therapy.* (1, 1929; 5, 1933)

Rothemund, Paul W. K., Dipl.-Ing., Dr.-Ing. (Munich). Antioch College, Yellow Springs, O. *Associate Professor of Biochemistry, and Research Chemist, The C. F. Kettering Foundation, Antioch College; Associate Professor (Non-resident), Department of Chemistry, Ohio State University.* (2, 1940)

Rous, Peyton, M.D., Sc.D. Rockefeller Institute for Medical Research, York Ave. at 66th St., New York City. *Member; Member of the National Academy of Sciences.* (4, 1913)

Routh, Joseph I., M.S., Ph.D. Chemistry Department, State University of Iowa, Iowa City. *Assistant Professor of Biochemistry.* (2, 1942)

Rovenstine, Emery Andrew, M.D. 477 First Ave., New York, N. Y. *Professor of Anesthesia, New York University; Director, Division of Anesthesia, Bellevue Hospital* (3, 1944)

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Sampson, Myra, A.M., Ph.D. Smith College, Northampton, Mass. *Professor and Chairman of Department of Zoology.* (5, 1935)

Samuels, Leo T., Ph.D. University of Utah Medical School, Salt Lake City. *Professor and Head of Dept. of Biochemistry.* (2, 1941; 3, 1937)

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Sandiford, Irene, Ph.D. Billings Hospital, University of Chicago, Chicago, Ill. *Assistant Professor of Medicine.* (2, 1925; 5, 1933)

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Sanford, Arthur H., A.M., M.D. Clinical Laboratories, Mayo Clinic, Rochester, Minn. *Head, Division of Clinical Laboratories.* (6, 1920)

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Saphir, Otto, M.D. Michael Reese Hospital, 29th St. and Ellis Ave., Chicago 16, Ill. *Pathologist, Michael Reese Hospital; Professor of Pathology, University of Illinois Medical School.* (4, 1927)

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Saslow, George, Ph.D., M.D. Department of Neuropsychiatry, Washington University Medical School, 640 South Kingshighway, St. Louis, Mo. *Assistant Professor of Psychiatry.* (1, 1936)

Satterfield, George H., A.M. State College of Agriculture and Engineering, University of North Carolina, Raleigh. *Professor of Biochemistry.* (2, 1944; 5, 1941)

Saul, Leon Joseph, M.A., M.D. Sanders Rd., North Brook, Ill. (1, 1933)

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Sawyer, Wilbur A., M.D., 4612 Drummond Ave., Chevy Chase, Md. *Director of Health, United Nations Relief and Rehabilitation Administration.* (4, 1930; 6, 1935)

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Schlenk, Fritz, Ph.D. University of Texas; M. D. Anderson Hospital of Cancer Research, Houston. *Biochemist.* (2, 1942)

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Schmitt, Francis Otto, Ph.D. Dept. of Biolo and Public Health, Massachusetts Institute Technology, Cambridge. *Professor of Biolo* (1, 1930)

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Schneider, Edward C., Ph.D., Sc.D., M.P.E. Gordon Place, Middletown, Conn. *Universi Professor, Wesleyan University.* (1, 1912; 2, 191

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Schroeder, E. F., M.S., Ph.D. G. D. Searle Co., P. O. Box 5110, Chicago 80, Ill. *Researc Biochemist.* (2, 1938)

Schuck, Cecelia, Ph.D. Purdue Universit Lafayette, Ind. *Professor of Nutrition, D partment of Home Economics.* (5, 1941)

Schultz, Edwin William, M.D. 743 Cooksey Lan Stanford University, Calif. *Professor of Ba teriology and Experimental Pathology.* (4, 192 6, 1928)

Schultz, Mark P., A.M., M.D. National Institute of Health, Bethesda, Md. *Surgeon, U. S. Public Health Service.* (6, 1933)

Schultz, W. H., Ph.D. 3102 18th St., N.W., Washington, D. C. *Professor of Pharmacology, Emeritus, University of Maryland.* (1, 1907; 3, 1909)

Schultze, Max O., Ph.D. Department of Chemistry, University of Pittsburgh, Pittsburgh, Pa. *Research Fellow, Buhl Foundation.* (2, 1938)

Schwartze, Erich W., M.D. 1225 Talbert St., S. E., Washington, D. C. (3, 1920)

Schweizer, Malvina, Ph.D.* Washington Square College of Arts and Sciences, New York University, New York, N. Y. *Instructor in Biology.* (1, 1944)

Scott, David Alymer, M.A., Ph.D. Connaught Laboratories, University of Toronto, Toronto 5, Ontario, Canada. *Senior Research Chemist.* (2, 1935)

Scott, Ernest L., Ph.D. 64 South St., Bogota, N. J. *Associate Professor of Physiology, Emeritus, Columbia University.* (1, 1914; 2, 1915)

Scott, Frederick Hughes, Ph.D., Sc.D., M.B. University of Minnesota, Minneapolis. *Professor of Physiology, Emeritus.* (1, 1908; 2, 1909)

Scott, John C., Ph.D. Hahnemann Medical College, Philadelphia, Pa. *Professor of Physiology and Head of the Department.* (1, 1936)

Scott, R. W., A.M., M.D. City Hospital, Cleveland, O. *Professor of Clinical Medicine, Western Reserve University; Physician-in-chief, Cleveland City Hospital.* (1, 1917; 3, 1917)

Scott, V. Brown, Ph.D., M.D. Inlow Clinic, Shelbyville, Ind. *Internist, Division of Medicine.* (1, 1941)

Scott, W. J. Merle, M.D. University of Rochester Medical School, Rochester, N. Y. *Associate Professor of Surgery.* (4, 1925)

Scott, W. W., M.D.* University Clinics, University of Chicago, Chicago, Ill. *Instructor in Surgery.* (1, 1943)

Scudi, John Vincent, Ph.D. Merck & Co., Inc., Rahway, N. J. *Biochemist.* (2, 1942)

Seager, Lloyd D., M.S., M.D. Woman's Medical College of Pennsylvania, East Falls, Philadelphia. *Professor of Pharmacology and Toxicology.* (3, 1939)

Sealock, Robert R., Ph.D. Department of Vital Economics, University of Rochester Medical School, Crittenden Blvd., Rochester, N. Y. *Assistant Professor of Physiological Chemistry.* (2, 1940; 5, 1941)

Seastone, C. V., Jr., M.D. University of Wisconsin Medical School, Madison. *Associate Professor of Medical Bacteriology.* (6, 1939)

Sebrell, W. H., Jr., M.D. National Institute of Health, Bethesda, Md. *Chief, Division of Physiology.* (2, 1938; 5, 1937)

Seecof, David P., M.D. 1970 Daly Ave., Bronx, New York City. (4, 1927)

Seegal, David, M.D. Welfare Island, New York City. *Director, Research and Clinical Service, First Division, Welfare Hospital; Associate Professor of Medicine, Columbia University.* (6, 1930)

Seegers, Walter H., Ph.D. Research and Biological Laboratories, Parke Davis & Co., Detroit, Mich. *Research Biochemist.* (2, 1941)

Seevers, Maurice Harrison, Ph.D., M.D. University of Michigan School of Medicine, Ann Arbor. *Professor of Pharmacology and Chairman of the Department.* (1, 1933; 3, 1930)

Seibert, Florence B., Ph.D., Sc.D., LL.D. Henry Phipps Institute, University of Pennsylvania, 7th and Lombard Sts., Philadelphia. *Associate Professor of Biochemistry.* (2, 1925)

Seidell, Atherton, M.S., Ph.D. 2301 Connecticut Ave., Washington, D. C. *Special Expert, National Institute of Health.* (2, 1924)

Seifter, Joseph, M.D. Wyeth Institute of Applied Biochemistry, Philadelphia, Pa. *Chief Pharmacologist.* (3, 1940)

Selle, Wilber Arthur, Ph.D. Medical School, University of Texas, Galveston. *Associate Professor of Physiology.* (1, 1938)

Selye, Hans, M.D., Ph.D. Medical Building, McGill University, Montreal, Que., Canada. *Assistant Professor of Anatomy.* (1, 1934)

Sendroy, Julius, Jr., M.A., Ph.D. Mercy Hospital, 2537 Prairie Ave., Chicago, Ill. *Professor of Chemistry and Chairman of the Department of Experimental Medicine, Loyola University School of Medicine.* (2, 1928)

Sevag, M. G., Ph.D. Department of Bacteriology, University of Pennsylvania School of Medicine, Philadelphia. *Assistant Professor of Biochemistry in Bacteriology.* (6, 1941)

Sevringhaus, Elmer L., M.A., M.D. Wisconsin General Hospital, Madison. *Professor of Medicine, University of Wisconsin; Consultant in Clinical Chemistry, Wisconsin Psychiatric Institute; Chemist to Wisconsin General Hospital.* (2, 1923; 5, 1939)

Shaffer, Morris F., D. Phil. Department of Pathology and Bacteriology, School of Medicine, Tulane University of Louisiana, New Orleans. *Associate Professor.* (4, 1939; 6, 1937).

Shaffer, Philip A., Ph.D. Washington University Medical School, St. Louis 4, Mo. *Professor of Biological Chemistry and Dean of the School of Medicine; Member, National Academy of Sciences.* (1, 1906; 2, 1906; 5, 1935)

Shannon, James A., M.D., Ph.D. Welfare Hospital, Welfare Island, New York City. *Director of Research Service, Third (New York University) Medical Division, Welfare Hospital,*

Department of Medicine, New York University College of Medicine. (1, 1933)

Shapiro, Herbert, A.M., Ph.D. Radiation Laboratory M.I.T., Cambridge, Mass. *Staff Member.* (1, 1937)

Sharpless, George R., D.Sc. Henry Ford Hospital, Detroit, Mich. *Associate in Nutrition Research.* (5, 1942)

Shaw, Myrtle, M.S., Ph.D. 11 S. Lake Ave., Albany, N. Y. *Senior Bacteriologist, Division of Laboratories and Research, New York State Department of Health.* (6, 1937)

Shay, Harry, M.D.* Samuel S. Fels Fund, Medical Tower, Philadelphia, Penna. *Director, Medical Research Laboratory.* (1, 1944)

Shear, Murray, J., Ph.D. National Cancer Institute, Bethesda, Md. *Principal Biochemist.* (2, 1930)

Sheard, Charles, A.M., Ph.D. Mayo Foundation, Rochester, Minn. *Chief of the Division of Physics and Biophysical Research and Professor of Physiological Optics and Biophysics, University of Minnesota.* (1, 1925)

Sheehan, Donal, M.D., D.Sc. New York University College of Medicine, First Ave., New York City. *Professor of Anatomy and Director of Anatomical Laboratories.* (1, 1938)

Shemin, David, A.M., Ph.D. Columbia University, College of Physicians and Surgeons, 630 W. 168th St., New York City. *Instructor in Biochemistry.* (2, 1944)

Sheppard, Fay, M.S. University of Oklahoma Medical School, Oklahoma City. *Instructor in Biochemistry.* (2, 1936)

Sherman, Henry C., A.M., Ph.D., Sc.D. Columbia University, New York City. *Mitchell Professor of Chemistry and Executive Officer of the Department of Chemistry; Member, National Academy of Sciences.* (1, 1923; 2,1906; 5, 1933)

Sherwin, Carl Paxson, Sc.D., M.D., Dr.P.H., LL.D. 40 E. 61st St., New York City. *Director of Metabolic Service, St. Vincent's Hospital; Associate Physician, French Hospital.* (1, 1919; 2, 1917)

Sherwood, Noble P., Ph.D., M.D. 1801 Indiana St., Lawrence, Kan. *Professor of Bacteriology, University of Kansas.* (6, 1928)

Sherwood, Thomas Cecil, M.A., Ph.D. 2639 Napoleon Ave., New Orleans, La. *House Physician, Southern Baptist Hospital.* (1, 1938)

Shideman, Frederick E., Ph.D. Dept. of Pharmacology, University of Michigan, Ann Arbor. *Instructor of Pharmacology.* (3, 1944)

Shimkin, Michael Boris, M.D. U. S. Public Health Service, National Cancer Institute, Bethesda, Md. *Passed Assistant Surgeon.* (4, 1940)

Shlaer, Simon, M.A., Ph.D. Columbia University, New York City. *Research Associate in Biophysics.* (1, 1938)

Shock, Nathan W., Ph.D. Unit on Gerontology, U. S. Public Health Service, Baltimore City Hospitals, Baltimore, Md. *Senior Psychophysiologist, U. S. Public Health Service, National Institute of Health, Bethesda, Md.* (1, 1942)

Shoemaker, Harold A., M.S., Ph.D. University of Oklahoma School of Medicine, 801 E. 13th St., Oklahoma City. *Assistant Dean; Professor of Pharmacology.* (3, 1941)

Shohl, Alfred T., M.D. 300 Longwood Ave., Boston, Mass. *Research Associate in Pediatrics, Harvard Medical School.* (2, 1922; 5, 1933)

Shope, Richard E., M.D. Department of Animal and Plant Pathology, The Rockefeller Institute, Princeton, N. J. *Member.* (4, 1934)

Shorr, Ephraim, M.D. The New York Hospital, 525 East 68th St., New York City. *Assistant Professor of Medicine, Cornell University Medical College; Assistant Attending Physician, The New York Hospital.* (1, 1931; 3, 1942)

Shwartzman, Gregory, M.D. 230 E. 50th St., New York City. *Head of Department of Bacteriology, Mount Sinai Hospital; Clinical Professor of Bacteriology, Columbia University.* (4, 1929; 6, 1930)

Sichel, F. J. M., Sc.M., Ph.D. College of Medicine, University of Vermont, Burlington. *Associate Professor of Physiology.* (1, 1939)

Sickles, Grace M., B.A. 2201 Twelfth St., Troy, N. Y. *Associate Bacteriologist, Division of Laboratories and Research, New York State Department of Health.* (6, 1932)

Sickles, Gretchen R., A.B. Division of Laboratories and Research, New York State Department of Health, Albany, N. Y. *Assistant Bacteriologist.* (6, 1937)

Siebert, Walter J., M.D. DePaul Hospital, St. Louis, Mo. *Director of Laboratories and Pathologist of DePaul and Lutheran Hospitals, St. Louis, and of St. Joseph Hospital, Alton, Ill.* (4, 1932)

Silberberg, Martin, M.D., Dr. med. habil. Snodgrass Laboratory of Pathology, City Hospital, 1428 Carroll St., St. Louis, Mo. (4, 1944)

Silberberg, Ruth, M.D. 235 E. 22nd St., New York, N. Y. *Assistant in Pathology, New York University, College of Medicine, New York.* (4, 1944)

Silvette, Herbert, M.S., Ph.D. University of Virginia Medical School, University. *Assistant Professor of Pharmacology.* (1, 1933; 3, 1940)

Simon, Frank A., M.D. 812 Heyburn Bldg., Louisville, Ky. (6, 1934)

Simonds, James P., Ph.D., M.D. Northwestern University Medical School, 303 E. Chicago Ave., Chicago, Ill. *Professor of Pathology.* (4, prior to 1920)

Simonson, Ernst, M.D. c/o Laboratory of Physiological Hygiene, Stadium South Tower, Uni-

versity of Minnesota, Minneapolis 14. *Associate Professor of Physiological Hygiene and of Physiology.* (1, 1941)

Sinclair, Robert Gordon, Ph.D. Queen's University, Kingston, Ont., Canada. *Professor of Biochemistry.* (2, 1931)

Sizer, Irwin W., Ph.D.* Massachusetts Institute of Technology, Cambridge. *Associate Professor of Physiology.* (1, 1944)

Slaughter, Donald, M.D. Southwestern Medical College, 2211 Oak Lawn, Dallas, Texas. *Dean of Students, Professor of Pharmacology, and Chairman of the Department of Physiology and Pharmacology.* (3, 1938)

Slonaker, James R., Ph.D. 334 Kingsley Ave., Palo Alto, Calif. *Professor of Physiology, Leland Stanford Junior University.* (1, 1917)

Smadel, Joseph Edwin, M.D. 3-30 Parsons Blvd., Malba, Long Island, N. Y. *Associate Member; Asst. Physician, Rockefeller Hospital.* (4, 1940; 6, 1937)

Small, James C., M.D. 133 S. 36th St., Philadelphia, Pa. *Instructor in Medicine, Graduate School of Medicine, University of Pennsylvania.* (4, 1927)

Smetana, Hans, M.D. College of Physicians and Surgeons, 630 W. 168th St., New York City. *Assistant Professor of Pathology.* (4, 1934)

Smith, Arthur H., M.S., Ph.D. Wayne University College of Medicine, Detroit 26, Mich. *Professor of Physiological Chemistry.* (1, 1923; 2, 1921; 5, 1933)

Smith, Austin Edward, M.D., C.M., M.Sc.(Med.). American Medical Association, 535 N. Dearborn St., Chicago, Ill. *Acting Secretary of the Council on Pharmacy and Chemistry, American Medical Association; Research Associate (Instructor) Dept. of Pharmacology, University of Chicago.* (3, 1942)

Smith, Clarence A., M.S., Ph.D. Standard Brands, Inc., 595 Madison Ave., New York City. *Technical Director, Special Products Department.* (1, 1921)

Smith, David T. Duke Hospital, Durham, N. C. (5, 1943)

Smith, Dietrich Conrad, A.M., Ph.D. University of Maryland School of Medicine, Lombard and Greene Sts., Baltimore. *Associate Professor of Physiology.* (1, 1937)

Smith, Elinor Van Dorn, Ph.D. 5 Middle St., Hadley, Mass. *Assistant Professor of Bacteriology, Smith College.* (6, 1940)

Smith, Elizabeth R. B., Ph.D. % Capt. Paul K. Smith, School of Aviation Medicine, Randolph Field, Texas. (2, 1938)

Smith, Erma A., A.M., Ph.D., M.D. Iowa State College, Ames. *Associate Professor of Physiology.* (1, 1928)

Smith, Fred M., M.D. State University of Iowa, Iowa City. *Professor of the Theory and Practice of Medicine and Head of the Department.* (1, 1925)

Smith, George H., M.A., Ph.D., M.A.(hon.), Sc.D. School of Medicine, Yale University, New Haven, Conn. *Professor of Immunology and Assistant Dean; Chairman, Department of Bacteriology, Yale University.* (6, 1918)

Smith, H. P., M.S., M.D. College of Medicine, State University of Iowa, Iowa City. *Professor of Pathology.* (1, 1937; 4, 1925)

Smith, Homer W., M.S., Sc.D. 477 First Ave., New York City. *Professor of Physiology, New York University College of Medicine.* (1, 1923; 2, 1930)

Smith, Lawrence Weld, M.D. Temple University School of Medicine, N. Broad St., Philadelphia, Pa. *Professor and Head of Department of Pathology; Director of Laboratories, Temple University Hospital.* (4, 1927)

Smith, Lee Irvin, A.M., Ph.D. School of Chemistry, University of Minnesota, Minneapolis. *Professor and Chief, Division of Organic Chemistry.* (2, 1942)

Smith, Margaret Cammack, A.M., Ph.D. University of Arizona, Tucson. *Professor of Nutrition; Nutrition Chemist, Agricultural Experiment Station, School of Home Economics.* (2, 1935; 5, 1933)

Smith, Maurice I., M.D. National Institute of Health, Bethesda, Md. *Principal Pharmacologist., U. S. Public Health Service.* (1, 1920; 3, 1916)

Smith, Paul K., Ph.D. AAF School of Aviation Medicine, Randolph Field, Texas. *Chief, Laboratory of Pharmacology and Biochemistry; Major, Air Corps.* (2, 1937; 3, 1937)

Smith, Paul W., M.S., Ph.D. School of Medicine, University of Oklahoma, 801 E. 13th St., Oklahoma City. *Assistant Professor of Pharmacology.* (1, 1933)

Smith, Philip Edward, M.S., Ph.D. 630 W. 168th St., New York City. *Professor of Anatomy, Columbia University; Member of the National Academy of Sciences.* (1, 1923)

Smith, Ralph G., M.D., Ph.D. Tulane University, Station 20, New Orleans, La. *Professor of Pharmacology.* (3, 1929)

Smith, R. Blackwell, Jr., S.M., Ph.D. Division of Pharmacology, Food and Drug Administration, Federal Security Agency, Washington, D. C. *Pharmacologist and Assistant to the Chief.* (3, 1944)

Smith, Susan Gower, M.A. Duke University, Durham, N. C. *Associate, Department of Medicine and Nutrition, School of Medicine.* (5, 1939)

Smith, Sybil L., A.M. Principal Experiment Station Administrator, Office of Experiment Stations, U.S.D.A., Washington, D. C. (5, 1940)

Smith, Wilbur Kenneth, M.D. University of Rochester School of Medicine and Dentistry,

260 Crittenden Blvd., Rochester, N. Y. *Associate Professor of Anatomy.* (1, 1939)

Smith, Willie W., M.A., Ph.D. 4710 Edgmoor Lane, Bethesda, Md. *Associate Physiologist, National Institute of Health.* (1, 1941)

Smithburn, Kenneth C., M.D. Yellow Fever Research Institute, P. O. Box 49, Entebee, Uganda, British East Africa. *Staff Member, International Health Division of The Rockefeller Foundation.* (6, 1937)

Smolens, Joseph, B.S. Dept. of Bacteriology, University of Pennsylvania Medical School, Philadelphia. *Fellow in Bacteriology.* (6, 1943)

Smythe, C. V., M.S., Ph.D. 5000 Richmond St., Philadelphia, Pa. *Head of Biochemistry, Rohm & Haas Company.* (2, 1934)

Snell, Albert M., M.D. Mayo Clinic, Rochester, Minn. *Head of Section on Medicine at Mayo Clinic; Professor in Medicine, Mayo Foundation Graduate School, University of Minnesota.* (4, 1930)

Snell, Esmond E., M.A., Ph.D. Department of Chemistry, University of Texas, Austin. *Assistant Professor of Chemistry and Research Biochemist.* (2, 1942)

Snyder, Charles D., M.S., Ph.D. Johns Hopkins University School of Medicine, Baltimore, Md. *Professor Emeritus of Experimental Physiology.* (1, 1907)

Snyder, Franklin Faust, M.D. University of Chicago, Ill. *Associate, Department of Obstetrics.* (1, 1936)

Sobel, Albert E., Ch.E., M.A., Ph.D. Jewish Hospital of Brooklyn, Prospect Place and Classon Ave., Brooklyn, N. Y. *Director of Chemical Laboratories; Lecturer in Biochemistry, Graduate Division, Brooklyn College; Lecturer in "Blood Chemistry", Hunter College.* (2, 1939)

Sobotka, Harry H., Ph.D. Mount Sinai Hospital, Fifth Ave. and 100th St., New York City. *Head, Department of Chemistry.* (2, 1932; 5, 1933)

Solandt, Donald Young, M.A., M.D., Ph.D. University of Toronto, Toronto, Ont., Canada. *Associate Professor of Physiology; Head of the Department of Physiological Hygiene.* (1, 1937)

Soley, Mayo H., M.D.* University of California Medical School, The Medical Center, San Francisco. *Associate Professor of Medicine and Lecturer in Pharmacology.* (1, 1943)

Sollmann, Torald, M.D. Sc.D., LL.D. School of Medicine, Western Reserve University, 2109 Adelbert Rd., Cleveland, O. *Dean and Professor of Pharmacology and Materia Medica, Emeritus.*

Somogyi, Michael, Ph.D. 216 S. Kingshighway, St. Louis, Mo. *Biochemist, Jewish Hospital of St. Louis.* (2, 1927)

Soskin, Samuel, M.D., M.A., Ph.D. Michael Reese Hospital, Chicago, Ill. *Director of Metabolic and Endocrine Research; Professoral Lecturer in Physiology, University of Chicago.* (1, 1930; 5, 1933)

Soule, Malcolm H., Sc.D., LL.D. University of Michigan, Ann Arbor. *Professor of Bacteriology, Director of the Hygienic Laboratory and Chairman of the Department of Bacteriology.* (4, 1927; 6, 1925)

Spain, Will C., M.D. 116 E. 53rd St., New York City. *Clinical Professor of Medicine, Post-Graduate Medical School, Columbia University.* (6, 1923)

Spealman, C. R., M.A., Ph.D. National Naval Medical Center, Bethesda, Md. (1, 1940)

Specht, Heinz, Ph.D. National Institute of Health, Rockville Pike, Bethesda, Md. *Associate Research Physiologist.* (1, 1941)

Sperry, Warren M., M.S., Ph.D. 722 W. 168th St., New York City. *Principal Research Biochemist, New York State Psychiatric Institute and Hospital; Assistant Professor of Biological Chemistry, College of Physicians and Surgeons, Columbia University.* (2, 1929; 5, 1933)

Spiegel, Ernest A., M.D. Temple University School of Medicine, Broad and Ontario Sts., Philadelphia, Pa. *Professor of Experimental Neurology.* (1, 1936)

Spiegel-Adolf, Mona, M.D. Temple University School of Medicine, Broad St. at Ontario Ave., Philadelphia, Pa. *Professor and Head of Department of Colloid Chemistry.* (2, 1933)

Spies, Tom D., M.D. Feb.-Nov. Hillman Hospital, Birmingham, Ala. Nov.-Feb. General Hospital, Cincinnati, O. *Associate Professor of Medicine, Univ. of Cincinnati College of Medicine. Visiting Professor of Medical Research, Univ. of Alabama School of Medicine. Professor of Medical Research, Univ. of Texas School of Medicine. Director, Nutrition Clinic, Hillman Hospital, Birmingham, Ala.* (3, 1941; 4, 1940; 5, 1938)

Spink, Wesley W., M.D. University of Minnesota Hospital, Minneapolis. *Associate Professor of Medicine, University of Minnesota Medical School.* (3, 1940; 4, 1940; 6, 1940)

Spohn, Adelaide, M.S., Ph.D. Elizabeth McCormick Memorial Fund, 848 N. Dearborn St., Chicago, Ill. (5, 1933)

Sproul, Edith E., M.D. Columbia University, College of Physicians and Surgeons, New York City. *Assistant Professor of Pathology.* (4, 1941)

Sprunt, Douglas H., M.D., M.S. Univ. of Tennessee, Memphis. *Professor of Pathology.* (4, 1934; 6, 1936)

Stadie, William C., M.D. 821 Maloney Clinic, 36th and Spruce Sts., Philadelphia, Pa. *Professor of Research Medicine, University of Pennsylvania.* (2, 1922)

Stainsby, Wendell J., M.D., C.M. Geisinger Memorial Hospital, Danville, Pa. *Chief Physician.* (6, 1930)

Stanley, Wendell M., M.S., Ph.D., Sc.D. Rockefeller Institute for Medical Research, Princeton, N. J. *Member; Member, National Academy of Sciences.* (2, 1936)

Stannard, James Newell, Ph.D. Research Division, Bureau of Medicine and Surgery, Navy Department, Washington 25, D. C. *Lieutenant, H-V(5), USNR.* (1, 1938)

Stare, Fredrick J., Ph.D., M.D. Department of Biological Chemistry, Harvard Medical School, Boston, Mass. *Assistant Professor of Nutrition.* (2, 1937; 5, 1942)

Starr, Isaac, M.D. 817 Maloney Clinic, Hospital of the University of Pennsylvania, Philadelphia. *Hartzell Research Professor of Therapeutics.* (1, 1929; 3, 1942)

Stavraky, George W., M.D., C.M., M.Sc. Medical School, University of Western Ontario, London, Ont., Canada. *Associate Professor of Physiology.* (1, 1937; 3, 1944)

Stearns, Genevieve, Ph.D. College of Medicine, State University of Iowa, Iowa City. *Research Professor of Pediatrics.* (2, 1932; 5, 1937)

Steel, Matthew, Ph.D. Long Island College of Medicine, 350 Henry St., Brooklyn, N. Y. *Professor of Biological Chemistry.* (2, 1909)

Steele, J. Murray, M.D. Welfare Hospital, Welfare Island, New York City. *Associate Professor of Medicine, New York University; Director 3rd (New York University) Medical Division of Welfare Hospital.* (1, 1936)

Steenbock, Harry, M.S., Ph.D., Sc.D. University of Wisconsin, Madison. *Professor of Biochemistry.* (2, 1912; 5, 1933)

Steggerda, F. R., M.A., Ph.D. 416 Natural History Building, University of Illinois, Urbana. *Assistant Professor of Physiology.* (1, 1934)

Stehle, Raymond Louis, A.M., Ph.D. Faculty of Medicine, McGill University, Montreal, Canada. *Professor of Pharmacology.* (2, 1920; 3, 1922)

Steigmann, Frederick, M.S., M.D. 348 S. Hamlin Ave., Chicago, Ill. *Associate in Medicine, College of Medicine, University of Illinois; Associate Attending Physician, Cook County Hospital.* (3, 1942)

Steiman, S. E., M.A., Ph.D., M.D. 364 Riverway, Boston, Mass. *Assistant Physician, Metropolitan State Hospital, Waltham, Mass.* (1, 1939)

Steinbach, H. Burr, M.A., Ph.D. Washington University, St. Louis, Mo. *Associate Professor of Zoology.* (1, 1934)

Steinberg, Bernhard, M.D. Toledo Hospital Institute of Medical Research, Toledo, O. *Director of the Toledo Hospital Institute of Medical Research; Director of Clinical and Morbid Pathological Laboratories, The Toledo Hospital; Surgeon, U.S.P.H. (inactive).* (4, 1928)

Steiner, Paul E., M.D. The University of Chicago, Chicago, Ill. *Associate Professor of Pathology.* (4, 1939)

Steinhardt, Jacinto, A.M., Ph.D. 1548 East-West Highway, Silver Spring, Md. *Research Associate, Division of War Research, Columbia University, New York City. Field Service Consultant, Office of Scientific Research and Development. (On loan to U. S. Navy.)* (2, 1939)

Steinhaus, Arthur H., M.S., Ph.D., M.P.E. 5315 Drexel Ave., Chicago, Ill. *Professor of Physiology, George Williams College, Hyde Park.* (1, 1928)

Stekol, Jakob A., M.A., D.Sc. Route 1, Box 759, Grass Valley, Calif. *Captain, Sn. C.* (2, 1936)

Stern, Kurt G., Ph.D. 85 Livingston St., Brooklyn, N. Y. *Adjunct Professor, Department of Chemistry, Polytechnic Institute.* (2, 1938)

Stetten, DeWitt, Jr., M.D., Ph.D. 630 W. 168th St., New York City. *Assistant Professor of Biochemistry, College of Physicians and Surgeons, Columbia University.* (2, 1944)

Stevens, S. Smith, Ph.D. Emerson Hall, Harvard University, Cambridge, Mass. *Assistant Professor of Psychology.* (1, 1937)

Stewart, Fred W., M.D. Memorial Hospital, 444 E. 68th St., New York City. *Pathologist; Associate Professor of Surgical Pathology, Cornell Medical School; Pathologist, New York State Department of Public Health, Division of Laboratories and Research.* (4, 1928)

Stewart, Harold L., M.D. The National Cancer Institute, Bethesda, Md. *Senior Pathologist.* (4, 1936)

Stewart, Winifred Bayard, M.D., M.A. 2028 Delancey St., Philadelphia, Pa. *Professor of Neurology, Woman's Medical College of Pennsylvania.* (1, 1941)

Stickney, J. Clifford, M.S., Ph.D.* West Virginia University School of Medicine, Morgantown. *Instructor in Physiology.* (1, 1944)

Stiebeling, Hazel K., M.A., Ph.D. United States Department of Agriculture, Washington, D. C. *Senior Food Economist, Bureau of Home Economics.* (5, 1933)

Stier, Theodore J. B., Ph.D. Indiana University Medical School, Bloomington. *Associate Professor of Physiology.* (1, 1938)

Still, Eugene U., Ph.D. % Strong Cobb & Co., 2654 Lisbon Rd., Cleveland, O. (1, 1929)

Stillman, Ernest G., M.D. 45 E. 75th St., New York City.

Stockton, Andr[illegible]ton, M.D. Barracks Dispensary, U. S. [illegible]val Supply Depot, Oakland, Calif. *Assistant Clinical Professor of Medicine, Stanford Medical School; Commander, (M.C.) U.S.N.R.* (3, 1931)

Stokstad, E. L. Robert, Ph.D. Lederle Laboratories, Pearl River, N. Y. *Research Chemist.* (5, 1942)

Stoland, O. O., M.S., Ph.D. 1845 Learnard Ave., Lawrence, Kan. *Professor of Physiology and Pharmacology, University of Kansas.* (1, 1913)

Stormont, Robert T., Ph.D. Naval Medical Research Institute, Bethesda, Md. *Lieutenant (j.g.) (M.C.) U.S.N.R.* (3, 1941)

Stotz, Elmer H., Ph.D. New York State Agricultural Experiment Station, Cornell University, Geneva, N. Y. *Professor of Agricultural and Biological Chemistry, Cornell University.* (2, 1939)

Stoughton, Roger W., M.S., Ph.D. Mallinckrodt Chemical Works, 3600 N. Second St., St. Louis, Mo. *Research Chemist.* (3, 1939)

Strong, Frank M., M.A., Ph.D. Department of Biochemistry, University of Wisconsin, Madison. *Associate Professor of Biochemistry.* (2, 1941)

Struck, Harold Carl, Ph.D. University of Illinois College of Medicine, 1853 W. Polk St., Chicago. *Assistant Professor of Pharmacology and Therapeutics.* (1, 1940)

Stuart, Charles A., M.Sc., Ph.D. 372 Lloyd Ave., Providence, R. I. *Associate Professor of Biology, Brown University.* (6, 1935)

Sturgis, Cyrus Cressey, M.D. Simpson Memorial Institute, Ann Arbor, Mich. *Director, Thomas Henry Simpson Memorial Institute for Medical Research; Chairman, Department of Medicine, University Hospital, and Professor of Medicine, University of Michigan.* (4, 1927)

SubbaRow, Y., Ph.D. Lederle Laboratories, Pearl River, N. Y. (2, 1939)

Sugg, John Y., Ph.D. Cornell University Medical College, 1300 York Ave., New York City. *Assistant Professor of Bacteriology and Immunology.* (6, 1938)

Sullivan, Michael Xavier, Ph.D. Chemo-Medical Research Institute, Georgetown University, 37th & O Sts., N. W., Washington, D. C. *Director and Research Professor of Chemistry.* (2, 1909)

Sulzberger, Marion B., M.D. 962 Park Ave., New York City. *Lieutenant Commander, M.C., U.S.N.R., in charge of Dermatology and Syphilology, U. S. Naval Hospital, Brooklyn, N. Y.; Assistant Clinical Professor of Dermatology and Syphilology, Columbia University.* (6, 1936)

Summerson, William H., M.A., Ph.D. Cornell University Medical College, 1300 York Ave., New York City. *Assistant Professor of Biochemistry.* (2, 1942)

Sumner, James Batcheller, A.M., Ph.D. Dairy Building, Ithaca, N. Y. *Professor of Biochemistry, Cornell University Medical College.* (2, 1919)

Sumwalt, Margaret, M.S., Ph.D. Medical School, University of Pennsylvania, Philadelphia. (1, 1934)

Sunderman, F. William, M.D., Ph.D. University of Pennsylvania, Philadelphia. *Assistant Professor of Research Medicine.* (2, 1931)

Sundstroem, Edward S., M.D. University of California, Berkeley. *Professor of Biochemistry.* (2, 1919)

Sure, Barnett, M.S., Ph.D. University of Arkansas, Fayetteville. *Head of Department and Professor of Agricultural Chemistry.* (2, 1923; 5, 1933)

Sutherland, George F., C.M., M.D., M.Sc. Crile General Hospital, Cleveland, O. *Major, M.C.* (1, 1939)

Sutton, T. Scott, M.Sc., Ph.D. Ohio State University, Columbus. *Assistant Professor; Associate, Ohio Agricultural Experiment Station, College of Agriculture.* (5, 1936)

Swain, Robert E., M.S., Ph.D., LL.D. 634 Mirada Ave., Stanford University, Calif. *Professor Emeritus of Chemistry.* (2, 1909)

Swann, Howard G., M.S., Ph.D. Dept. of Pharmacology, University of Texas Medical School, Galveston. *Assistant Professor of Physiology. Captain, Aero Medical Laboratory, Wright Field, Dayton, O.* (1, 1940)

Swanson, Pearl P., M.S., Ph.D. Iowa State College, Ames. *Professor of Foods and Nutrition, Dept. of Foods and Nutrition.* (5, 1933)

Swanson, William W., M.S., M.D. 2376 E. 71st St., Chicago, Ill. (2, 1938)

Sweeney, H. Morrow, M.S., Ph.D. School of Medical Sciences, University of South Dakota, Vermillion. *Professor of Physiology and Pharmacology and Head of the Department.* (1, 1939)

Sweet, J. E., A.M., M.D., Sc.D. Unadilla, N. Y. *Emeritus Professor of Surgical Research, Cornell Medical College.* (1, 1913)

Swift, Homer, M.D., D.Sc. 888 Park Ave., New York City. *Member, Rockefeller Institute for Medical Research; Physician to The Hospital of The Rockefeller Institute for Medical Research.* (6, 1920)

Swift, Raymond W., M.S., Ph.D. Pennsylvania State College, State College. *Professor, Institute of Animal Nutrition.* (5, 1934)

Swingle, Wilbur Willis, Ph.D. Princeton University, Princeton, N. J. *Professor of Biology.* (1, 1924)

Sydenstricker, V. P. University of Georgia School of Medicine, Augusta. *Professor of Medicine.* (5, 1944)

Sykes, Joseph F., M.S.A., Ph.D. Michigan State College, E. Lansing. *Research Assistant and Assistant Professor of Physiology and Pharmacology.* (1, 1942)

Syverton, Jerome T., M.D. The University of Rochester School of Medicine and Dentistry and Strong Memorial Hospital, Rochester, N. Y. *Associate Professor of Bacteriology.* (4, 1940)

Tainter, M. L., M.A., M.D. Winthrop Chemical Company, Rensselaer, N. Y. *Director of Research.* (1, 1929; 3, 1927)

Tait, John, M.D., D.Sc., F.R.S.E., F.R.S.C. McGill University, Montreal, Que., Canada. *Professor of Physiology (Retired).* (1, 1919)

Talbert, George A., Ph.D. University Station, Grand Forks, N. D. *Professor of Physiology and Pharmacology, University of North Dakota.* (1, 1919)

Talbot, Samuel Armstrong, A.M., M.S., Ph.D. Wilmer Institute, Johns Hopkins Hospital, Baltimore, Md. *Instructor in Physiological Optics, Johns Hopkins University.* (1, 1940)

Taliaferro, William H., Ph.D. Department of Bacteriology, University of Chicago, Chicago, Ill. *Eliakim H. Moore Distinguished Service Professor of Parasitology and Dean of the Division of Biological Sciences.* (6, 1930)

Tannenbaum, Albert, M.D. Michael Reese Hospital, 29th St. & Ellis Ave., Chicago, Ill. *Director, Department of Cancer Research.* (4, 1942)

Tashiro, Shiro, Ph.D., M.D. College of Medicine, University of Cincinnati, Cincinnati, O. *Professor of Biochemistry.* (1, 1913; 2, 1913)

Tatum, Arthur L., M.S., Ph.D., M.D. University of Wisconsin, Madison. *Professor of Pharmacology.* (1, 1913; 3, 1919)

Tauber, Henry, Ph.D. 1909 S. Sixth St., Philadelphia, Pa. *Publicker Commercial Alcohol Company, Supervisor of Ethyl Alcohol Fermentation.* (2, 1933)

Taylor, Alonzo E., M.D. General Mills, Inc. 200 Chamber of Commerce, Minneapolis, Minn. *Director of Research. Director Emeritus, Food Research Institute, Stanford University.* (5, 1933)

Taylor, Alton R., Ph.D. Duke University School of Medicine, Durham, N. C. *Research Associate in Experimental Surgery.* (6, 1943)

Taylor, Fred A., Ph.D. 320 E. North Ave., N.S., Pittsburgh, Pa. *Biochemist, Singer Memorial Laboratory.* (2, 1933)

Taylor, Haywood M., M.S., Ph.D. Duke University School of Medicine, Durham, N. C. *Associate Professor of Biochemistry and Toxicology; Toxicologist to Duke Hospital.* (4, 1942)

Taylor, Henry Longstreet, Ph.D.* University of Minnesota, Minneapolis. *Associate Physiologist, Laboratory of Physiological Hygiene.* (1, 1944)

Taylor, John Fuller, Ph.D. Washington University School of Medicine, Euclid and Kingshighway, St. Louis, Mo. *Assistant Professor in Biological Chemistry.* (2, 1944)

Taylor, M. Wight. New Jersey Agricultural Exper. Station, New Brunswick. *Assoc. Biochem. in Nutr., and Assoc. Prof. of Agr. Biochem., Rutgers Univ.* (5, 1944)

Taylor, Norman Burke, M.D., F.R.S. (Can.), M.R.C.S. (Eng.), L.R.C.P. (Lon.), F.R.C.S. (Edin.), F.R.C.P. (Can.). University of Toronto, 5, Ontario, Ont., Canada. *Professor of Physiology.* (1, 1922)

Teague, Robert S., M.D., Ph.D. Department of Pharmacology and Physiology, University of Alabama, University. *Instructor in Pharmacology.* (3, 1942)

Templeton, Roy D., B.S. 5630 South Flores, San Antonio, Texas. (1, 1935)

Ten Broeck, Carl, M.D. The Rockefeller Institute for Medical Research, Department of Animal and Plant Pathology, Princeton, N. J. *Member.* (4, 1932; 6, 1924)

Tepperman, Jay, M.D.* 70 Howe St., New Haven 11, Conn. Yale University School of Medicine, 333 Cedar St., New Haven, Conn. *Research Assistant, Instructor Rank.* (1, 1944)

Terplan, Kornel L., M.D. University of Buffalo, School of Medicine, Buffalo, N. Y. *Professor of Pathology and Bacteriology.* (4, 1935)

Thannhauser, S. J., M.D., Ph.D. Tufts College Medical School, 30 Bennet St., Boston, Mass. *Clinical Professor of Medicine; Associate Physician in Chief, Joseph H. Pratt Diagnostic Hospital.* (2, 1937)

Thayer, Sidney Allen, Ph.D. 1402 S. Grand Blvd., St. Louis 4, Mo. *Associate Professor of Biochemistry, St. Louis University School of Medicine.* (2, 1933)

Theiler, Max, M.D. Rockefeller Foundation, New York City. *Member of Field Staff.* (4, 1938)

Thienes, Clinton H., A.M., M.D., Ph.D. University of Southern California School of Medicine, Los Angeles. *Professor of Pharmacology.* (3, 1928)

Thomas, Arthur W., Ph.D. Columbia University, New York City. *Professor of Chemistry.* (2, 1924)

Thomas, Byron H., M.S., Ph.D. Iowa State College, Ames. *Professor and Head, Animal Chemistry and Nutrition, Iowa Agricultural Experiment Station.* (5, 1933)

Thomas, Caroline Bedell, M.D. The Johns Hopkins Hospital, Baltimore, Md. *Instructor in Medicine, Johns Hopkins University School of Medicine.* (1, 1939)

Thomas, J. Earl, M.S., M.D. Jefferson Medical College, Philadelphia, Pa. *Professor of Physiology.* (1, 1922; 3, 1924)

Thompson, Marvin Russell, Ph.C., M.Ph., (Hon.) Ph.D. 113 W. 18th St., New York, N. Y. *President, William R. Warner and Co., Inc.; President, Gustavus and Louise Pfeiffer Research Foundation; Director, Warner Institute for Therapeutic Research; Trustee, Columbia University College of Pharmacy; Trustee, and Assistant*

Secretary, Medical Memorial Fund Inc. (3, 1944)

Thompson, Randall L., S.M., Sc.D., M.D. School of Medicine, Western Reserve University, 2109 Adelbert Rd., Cleveland, O. *Assistant Professor of Bacteriology.* (6, 1937)

Thompson, William R., Ph.D. 1 Darrock Rd., Delmar, N. Y. *Senior Biochemist, Division of Laboratories and Research, New York State Department of Health.* (2 1934)

Thomson, David Landsborough, M.A., Ph.D., F.R.S.C. McGill University, Montreal, Canada. *Professor of Biochemistry and Dean of the Faculty of Graduate Studies and Research.* (2, 1929)

Thorn, George Widmer, M.D. Peter Bent Brigham Hospital, Boston, Mass. *Professor of Medicine of Harvard University.* (1, 1939)

Tillett, William S., M.D., Sc.D. (hon.). Department of Bacteriology, New York University College of Medicine, 477 First Ave., New York City. *Professor of Medicine.* (6, 1927)

Tilt, Jennie, M.S., Ph.D. Florida State College for Women, Tallahassee. *Professor of Physiological Chemistry and Nutrition.* (5, 1937)

Tipson, R. Stuart, Ph.D. Mellon Institute of Industrial Research, University of Pittsburgh, Pittsburgh, Pa. *Fellow, Department of Research in Pure Chemistry.* (2, 1937)

Tipton, Samuel R., Ph.D. Box 1961, University, Alabama. *Associate Professor of Physiology and Pharmacology, University of Alabama, School of Medicine.* (1, 1940)

Tisdall, Frederick F., M.S., M.D., M.R.C.S., L.R.C.P. (London), F.R.C.P. (C.). University of Toronto, Toronto, Canada. *Associate Professor of Pediatrics; Associate Physician, Hospital for Sick Children, Department of Medicine, University of Toronto.* (2, 1922; 5, 1933)

Titus, Harry W., A.M., Ph.D. c/o Limestone Products Corp. of America, Newton, N. J. *Technical Counsellor.* (2, 1929; 5, 1933)

Tobias, Julian M., M.D.* University of Chicago, Chicago, Ill. *Instructor in Physiology. On leave to Medical Research Laboratory, Edgewood Arsenal, Md.* (1, 1944)

Tocantins, Leandro Maués, M.D. Jefferson Medical College, Philadelphia, Pa. *Associate Professor of Medicine.* (1, 1939)

Todhunter, Elizabeth Neige, M.Sc., Ph.D., University of Alabama, University. *Associate Professor of Nutrition.* (5, 1939)

Toennies, Gerrit, Ph.D. Lankenau Hospital Research Institute, Philadelphia, Pa. *Research Chemist.* (2, 1934)

Tolle, Chester D., Ph.D. Food and Drug Administration, Federal Security Agency, Washington, D. C. *Senior Biochemist.* (5, 1942)

Tompkins, Edna H., M.D. Laboratory of Applied Physiology, Yale University, 4 Hillhouse Ave., NewHaven, Conn. *Research Associate; Associate Professor.* (4, 1941)

Toomey, John A., M.D., LL.B. Division of Contagious Diseases, City Hospital, 3395 Scranton Rd., Cleveland, O. *Associate Professor of Pediatrics (Contagious Diseases), Western Reserve University School of Medicine.* (6, 1943)

Torda, Clara, Ph.D., M.D.* Cornell Medical Center, New York City. *Research Fellow in Department of Medicine.* (1, 1943; 3, 1944)

Torrey, John C., Ph.D., D.Sc. 1300 York Ave., New York City. *Professor (Emeritus) of Epidemiology, Cornell University Medical College.* (6, 1920)

Toth, Louis A., M.S., Ph.D. Tulane University School of Medicine, New Orleans, La. *Assistant Professor of Physiology; Captain A.C.-33d Altitude Training Unit SAAAB, Santa Ana, Calif.* (1, 1940)

Tourtellotte, Dee, M.S., D.Sc. Charles B. Knox Gelatin Co., Johnstown, N. Y. (5, 1935)

Tower, Sarah Sheldon, M.D., Ph.D. Johns Hopkins Medical School, Baltimore, Md. *Associate in Anatomy.* (1, 1932)

Travell, Janet, M.D. Cornell University Medical College, New York City. *Instructor in Pharmacology.* (3, 1933)

Travis, Lee Edward, A.M., Ph.D. University of Southern California, Los Angeles. *Professor of Psychology and Director of the Psychological Center; Major, YAAF (Yuma, Ariz.).* (1929)

Treadwell, Carleton R., M.S., Ph.D. Southwestern Medical College, 2211 Oak Lawn Ave., Dallas, Texas. *Associate Professor of Biochemistry* (2, 1944)

Treffers, Henry P., Ph.D. Harvard Medical School, Boston, Mass. *Assistant Professor of Comparative Pathology and Biochemistry.* (1942)

Trimble, Harry C., M.D., Ph.D. 25 Shattuck St., Boston Mass. *Assistant Professor of Biological Chemistry, Harvard Medical School.* (2, 1929; 5, 1936)

Tuft, Louis H., M.D. 1530 Locust St., Philadelphia, Pa. *Assistant Professor of Medicine, Temple University Medical School; Chief of Clinic of Allergy and Applied Immunology, Temple University Hospital.* (6, 1928)

tum Suden, Caroline, M.A., Ph.D. 80 E. Concord St., Boston, Mass. *Evans Research Fellow in Physiology, Boston University School of Medicine; Assistant, Evans Memorial Staff, Massachusetts Memorial Hospitals.* (1, 1936)

Tuohy, Edward B., M.S., M.D. Percy Jones General Hospital, Battle Creek, Mich. *Assistant Professor of Anesthesiology, Mayo Foundation; Captain, M.C.* (3, 1941)

Turner, Abby H., Ph.D. Mount Holyoke College, South Hadley, Mass. *Professor of Physiology.* (1, 1928)

Turner, William A., Ph.D. Bureau of Dairy Industry, U. S. Department of Agriculture, Beltsville, Md. *Associate Chemist.* (2, 1929)

Tuttle, Waid Wright, M.A., Ph.D. State University of Iowa, Iowa City. *Professor of Physiology.* (1, 1925)

Tweedy, Wilbur R., Ph.D. Loyola University School of Medicine, 706 S. Wolcott St., Chicago, Ill. *Professor and Chairman, Department of Biological Chemistry.* (2, 1931)

Tyler, David B., Ph.D.* California Institute of Technology, Pasadena. *Hixon Fund Fellow.* (1, 1943)

Tyslowitz, Richard, M.D.* Schering Corporation, Bloomfield, N. J. *Head of the Biology Laboratory.* (1, 1944)

Unna, Klaus R. W., M.D. Merck Institute for Therapeutic Research, Rahway, N. J. *Research Associate.* (1, 1941; 3, 1944; 5, 1942)

Upton, Morgan, M.A., Ph.D. Dept. of Psychology, St. Lawrence University, Canton, N. Y. *Assistant Director, British Ministry of Supply Mission, 404 A Bradford Building, 1800 K. St., N.W., Washington, D. C.* (1, 1934)

Urban, Frank, Ph.D. Washington University School of Medicine, St. Louis, Mo. *Assistant Professor of Biochemistry.* (2, 1932)

Vahlteich, Ella McCollum, M.A., Ph.D. 46 Hudson Ave., Edgewater, N. J. (5, 1933)

Van Dyke, H. B., Ph.D., M.D. 630 W. 168th St., New York, N. Y. *Professor of Pharmacology, Columbia University, College of Physicians and Surgeons.* (1, 1925; 3, 1942)

Van Harreveld, Anthonie, M.A., M.D. California Institute of Technology, Pasadena. *Associate Professor of Physiology.* (1, 1941)

Van Liere, Edward J., M.S., M.D., Ph.D. The School of Medicine, West Virginia University, Morgantown. *Professor of Physiology and Dean.* (1, 1927)

Van Slyke, Donald D., Ph.D., Sc.D., M.D. Rockefeller Institute for Medical Research, 66th St. and York Ave., New York City. *Member; Member, National Academy of Sciences.* (2, 1908)

Van Wagenen, Gertrude, Ph.D. Yale University School of Medicine, New Haven, Conn. *Associate Professor.* (1, 1932)

Van Winkle, Walton, Jr., M.D. Drug Division, Food and Drug Administration, Federal Security Agency, Washington, D. C. *Senior Medical Officer.* (3, 1939)

Vars, Harry M., Ph.D. Harrison Department of Surgical Research, University of Pennsylvania Medical School, Philadelphia. *Assistant Professor of Physiological Chemistry.* (2, 1935; 5, 1935)

Vennesland, Birgit, Ph.D. Dept. of Biochemistry, University of Chicago, Chicago, Ill. *Assistant Professor.* (2, 1944)

Venning, Eleanor H., M.S., Ph.D. University Clinic, Royal Victoria Hospital, Pine Ave., Montreal, Quebec, Canada. *Research Fellow.* (2, 1938)

Vickery, Hubert B., M.S., Ph.D. Connecticut Agricultural Experiment Station, New Haven. *Lecturer on the Chemistry of Proteins, Yale University; Biochemist in Charge, Connecticut Agricultural Experiment Station; Member, National Academy of Sciences.* (2, 1923)

Victor, Joseph, M.D. Research Division for Chronic Disease, Welfare Island, N. Y. *Experimental Pathologist; Assistant Professor of Pathology, Columbia University College of Physicians and Surgeons.* (4, 1935)

Virtue, Robert W., Ph.D. 2134 E. Iliff Ave., Denver, Colo. *Associate Professor of Chemistry, University of Denver.* (2, 1939)

Visscher, Maurice B., M.S., Ph.D. University of Minnesota, Minneapolis. *Professor of Physiology.* (1, 1927)

Voegtlin, Carl, Ph.D. National Cancer Institute, Bethesda 14, Md. *Chief.* (1, 1908; 2, 1908; 3, 1908)

von Haam, Emmerich, M.D. Ohio State University, Columbus. *Professor of Pathology.* (4, 1938)

Von Oettingen, W. F., M.D., Ph.D. National Institute of Health, Division of Industrial Hygiene, Bethesda, Md. *Principal Industrial Toxicologist.* (3, 1925)

Vorwald, Arthur J., Ph.D., M.D. Lt. Commander, U.S.N.R., U. S. Naval Hospital, Annapolis, Md. (4, 1937)

Vos, Bert J., Ph.D., M.D. Division of Pharmacology, Food and Drug Administration, Washington, D. C. *Associate Pharmacologist.* (3, 1941)

Waddell, J. A., M.D. Monroe Hill, Medical School, University of Virginia, Charlottesville. *Professor of Pharmacology.* (3, 1916)

Waddell, James, Ph.D. E. I. duPont de Nemours & Co., New Brunswick, N. J. *Director of the Biological Laboratory.* (2, 1930; 5, 1935)

Wadsworth, Augustus B., M.D. New York State Department of Health, Albany. *Director, Division of Laboratories and Research.* (4, 1935; 6, 1920)

Waelsch, Heinrich, M.D., Ph.D. Columbia University, College of Physicians and Surgeons, 630 W. 168th St., New York City. *Research Associate in Biochemistry.* (2, 1941)

Waisman, Harry A., M.S., Ph.D. Biochemistry Bldg., University of Wisconsin, Madison. *Associate in Biochemistry.* (2, 1944)

Wakeman, Alfred J., Ph.D. Hatfield Hill Road, Bethany, Conn. *Retired.* (2, 1906)

Wakerlin, George E., Ph.D., M.D. University of Illinois Medical School, 1853 W. Polk St., Chicago. *Professor of Physiology.* (1, 1933; 3, 1934)

Wakim, Khalil G., M.D., Ph.D. University of Indiana Medical School, Bloomington. *Professor of Physiology.* (1, 1942)

Wald, George, M.A., Ph.D. Biological Laboratories, Harvard University, Cambridge, Mass. (1, 1934)

Walker, Arthur M., M.D. University of Pennsylvania, Philadelphia. *Associate Professor of Pharmacology, Major, M.C.* (1, 1932; 3, 1939)

Walker, Burnham S., Ph.D., M.D. Boston University School of Medicine, 80 E. Concord St., Boston, Mass. *Professor of Biochemistry.* (2, 1940)

Walker, Ernest Linwood, S.D. Second and Parnassus Aves., San Francisco, Calif. *Professor of Tropical Med., The George Williams Hooper Foundation for Medical Research, University of California.* (3, 1931)

Wallace, George B., A.M., Sc.D. (hon.) M.D. 477 First Ave., New York City. *Professor of Pharmacology, New York University College of Medicine.* (1, 1901; 2, 1906; 3, 1909)

Wallen-Lawrence, Zonja, Ph.D. 4534 W. Pine Blvd., St. Louis, Mo. *Lecturer on Nutrition and Diet, Washington University School of Dentistry.* (2, 1937)

Walter, Carl W., M.D. Harvard Medical School, 25 Shattuck Street, Boston, Mass. *Director, Laboratory for Surgical Research; Assistant Professor of Surgery, Harvard Medical School; Senior Associate in Surgery, Peter Bent Brigham Hospital.* (4, 1942)

Walters, Orville S., Ph.D., M.D. Central College, Buhler, Kan. *President.* (1, 1936)

Walton, Robert P., M.A., Ph.D., M.D. Medical College of the State of South Carolina, Charleston. *Professor of Pharmacology.* (3, 1933)

Walton, Seth T., V.M.D., M.S., Ph.D. City Health Department, Charlotte, N. C. *Director of Laboratories and Research.* (6, 1936)

Walzer, Matthew, M.D. 20 Plaza St., Brooklyn, N. Y. *Attending in Allergy, Jewish Hospital of Brooklyn.* (6, 1924)

Wang, Chi Che, M.S., Ph.D. 323 Belden Ave., Chicago, Ill. *Research Chemist, Children's Memorial Hospital; Assistant Professor, Dept. of Physiology, Northwestern University Medical College, Chicago.* (2, 1922; 5, 1933)

Wang, Shih-Chun, M.D., Ph.D.* Columbia University College of Physicians and Surgeons, 630 W. 168th St., New York City. *Assistant Professor in the Department of Physiology.* (1, 1943)

Wangensteen, Owen Harding, M.D. University of Minnesota, Minneapolis. *Professor of Surgery.* (4, 1931)

Warner, Emory D., M.D. Medical Laboratories Bldg., Iowa City, Ia. *Associate Professor of Pathology.* (4, 1937)

Warren, Charles O., Ph.D., M.D. Cornell University Medical College, 1300 York Ave., New York City. *Assistant Professor of Physiology and Anatomy.* (1, 1941)

Warren, Madeleine Field, A.M., Ph.D. 9 High Rock St., Needham, Mass. Harvard School of Public Health, 55 Shattuck St., Boston, Mass. *Associate in Physiology.* (1, 1933)

Warren, Shields, M.D. Palmer Memorial Hospital, 195 Pilgrim Rd., Boston, Mass. *Pathologist, New England Deaconess Hospital; Assistant Professor of Pathology, Harvard Medical School.* (4, 1929)

Wartman, William Beckman, M.D. Western Reserve University, 2085 Adelbert Rd., Cleveland, O. *Assistant Professor of Pathology.* (4, 1940)

Wasteneys, Hardolph, Ph.D., F.R.S.C. University of Toronto, Toronto, Canada. *Professor and Head of Department of Biochemistry.* (2, 1915)

Wastl, Helene, M.D. Hahnemann Medical College and Hospital, Philadelphia, Pa. *Research Associate in Pharmacology and Anatomy.* (1, 1939)

Waterman, Robert E., B.S. Schering Corporation, 86 Orange St., Bloomfield, N. J. (2, 1940)

Waters, Ralph Milton, M.D. 1300 University Ave., Madison, Wis. *Professor of Anesthesia, University of Wisconsin.* (3, 1937)

Watson, Cecil J., M.D., Ph.D. Department of Medicine, University Hospital, Minneapolis, Minn. *Professor and Head of Department of Medicine.* (4, 1941)

Watson, John B., A.M., Ph.D., LL.D. 420 Lexington Ave., New York City. *Vice President of the J. Walter Thompson Co.* (1, 1907)

Waud, Russell A., M.D., M.Sc., Ph.D. Medical School, University of Western Ontario, London, Canada. *Professor of Pharmacology.* (1, 1925; 3, 1931)

Waugh, David F., Ph.D.* Department of Biology and Biological Engineering, Massachusetts Institute of Technology, Cambridge. *Assistant Professor of Physical Biology.* (1, 1943)

Wearn, Joseph T., M.D. Lakeside Hospital, Cleveland, O. *Professor of Medicine, Western Reserve University; Director of Medicine, Lakeside Hospital.* (1, 1921)

Weatherby, J. H., M.A., Ph.D. Naval Air Station Dispensary, Pensacola, Fla. *Research Associate*

in Pharmacology, Medical College of Virginia; Lieutenant (M.C.) U.S.N.R. (3, 1941)

Weber, Clarence J., M.D., Ph.D. University of Kansas Hospitals, Kansas City. *Assistant Professor of Research Medicine.* (2, 1931)

Webster, Bruce, M.D., C.M. Cornell University Medical College, 1300 York Ave., New York City. *Assistant Professor Medicine; Associate Attending Physician, New York Hospital.* (5 1935)

Weed, Lewis H., A.M., M.D., Sc.D. Johns Hopkins University Medical School, Baltimore, Md. *Professor of Anatomy.* (1, 1919)

Wégria, René, M.D. Department of Medicine, Presbyterian Hospital, 622 W. 168th St., New York City. (1, 1941)

Weichert, Charles K., Ph.D. University of Cincinnati, Cincinnati, O. *Assistant Professor of Zoology.* (1, 1935)

Weil, Alfred J., M.D. Lederle Laboratories, Inc., Pearl River, N. Y. *Immunologist.* (6, 1940)

Weil, Arthur, M.D. 161 East 71st St., New York, N. Y. (4, 1940)

Weil, Leopold, Ph.D. Eastern Regional Research Laboratory, U. S. Department of Agriculture, Chestnut Hill Station, Philadelphia, Pa. *Associate Chemist.* (2, 1942)

Weir, Everett G., M.S., Ph.D. School of Medicine, Howard University, Washington, D. C. *Assistant Professor of Physiology.* (1, 1941)

Weiss, Charles, M.S., Ph.D., M.D. Jewish Hospital, York & Tabor Roads, Philadelphia, Pa. *Director of Laboratories.* (4, 1934; 6, 1920)

Weiss, Emil, M.D., Ph.D. P. O. Box 714, Chicago, Ill. *Pathologist, Chicago Eye, Ear, Nose and Throat Hospital.* (6, 1927)

Weiss, Paul, Ph.D. University of Chicago, Chicago, Ill. *Professor of Zoology.* (1, 1936)

Welch, Arnold D., Ph.D., M.D. Western Reserve University School of Medicine, Cleveland, O. *Professor of Pharmacology.* (3, 1942; 5, 1944)

Welch, Arnold DeMerritt, Ph.D., M.D. Medical Research Division, Sharp and Dohme, Inc., Glenolden, Pa. *Director of Research.* (3, 1942)

Welch, Henry, Ph.D. Bacteriological Section, U. S. Food and Drug Administration, Washington, D. C. *Senior Bacteriologist.* (6, 1932)

Weld, Charles Beecher, M.A., M.D. Dalhousie University, Halifax, N.S., Canada. *Professor of Physiology.* (1, 1936)

Weld, Mrs. Julia T. College of Physicians and Surgeons, 630 W. 168th St., New York City. *Research Associate in Pathology.* (6, 1920)

Welker, William H., A.C., Ph.D., D. Sc. 1853 W. Polk St., Chicago, Ill. *Professor of Biological Chemistry and Head of the Department, College of Medicine, University of Illinois.* (2, 1906)

Weller, Carl Vernon, M.D. 1130 Fair Oaks Parkway, Ann Arbor, Mich. *Professor of Pathology and Chairman, Department of Pathology, University of Michigan.* (4, 1923)

Wells, Herbert S., M.D. Bowman Gray School of Medicine, Winston-Salem, N. C. *Professor of Physiology and Pharmacology.* (1, 1932)

Wells, Joseph Albert, M.S., Ph.D. Northwestern University Medical School, Chicago, Ill. *Associate in Pharmacology.* (3, 1944)

Wendel, William B., Ph.D. College of Medicine, University of Tennessee, Memphis. *Associate Professor of Chemistry.* (2, 1932)

Werkman, C. H., Ph.D. Science Hall, Iowa State College, Ames. *Professor in Charge, Department of Bacteriology.* (2, 1942)

Werle, Jacob M., M.D.* 4478 Broadale Ave., Cleveland, O. *1st Lieutenant, M. C.* (1, 1943)

Werner, Harold W., Ph.D. The Wm. S. Merrell Co., Lockland Station, Cincinnati, O. *Director of Pharmacology Research.* (3, 1942)

Wertenberger, Grace E., S.M., Ph.D.* Women's Medical College of Pennsylvania, Philadelphia. *Assistant Professor of Physiology.* (1, 1943)

Wesson, Laurence Goddard, Ph.D. Forsyth Dental Infirmary, Boston, Mass. *Research Biochemist.* (2, 1929; 3, 1932)

West, Edward S., M.S., Ph.D. University of Oregon Medical School, Portland. *Professor of Biochemistry.* (2, 1925)

West, Randolph, M.A., M.D. 622 W. 168th St., New York City. *Associate Professor of Medicine, Columbia University.* (2, 1931)

Westerfeld, Wilfred Wiedey, Ph.D. Harvard Medical School, 25 Shattuck St., Boston, Mass. *Assistant Professor of Biological Chemistry.* (2, 1944)

Weymouth, Frank W., Ph.D. Stanford University, Calif. *Professor of Physiology and Executive of the Department.* (1, 1917)

Wheeler, George W., M.D. New York Hospital, 525 E. 68th St., New York City. *Superintendent.* (6, 1920)

Wheeler, Kenneth M., Ph.D. Bureau of Laboratories, Connecticut State Department of Health, 1179 Main St., Hartford. *Research Microbiologist.* (6, 1938)

Wheeler, Mary W., M.A. Division of Laboratories and Research, New York State Department of Health, Albany. *Associate Bacteriologist.* (6, 1933)

Wheeler, Ruth, Ph.D. P. O. Box 444, Annapolis, Md. (2, 1915; 5, 1933)

Wheelon, Homer, M.S., M.D. American Bank Bldg., Seattle, Wash. (1, 1919)

Whipple, George H., M.D., Sc.D. University of Rochester, Rochester, N. Y. *Professor of Pathology and Dean of the School of Medicine and*

Dentistry; Member of the National Academy of Sciences. (1, 1911; 4, 1913)

White, Abraham, M.A., Ph.D. 333 Cedar St., New Haven, Conn. *Associate Professor of Physiological Chemistry, Medical School, Yale University.* (2, 1934; 5, 1937)

White, Frank D., Ph.D., F.I.C. Medical College, University of Manitoba, Winnipeg, Canada. *Assistant Professor of Biochemistry, Faculty of Medicine.* (2, 1931)

White, Harvey Lester, M.D. Station Hospital, A.P.O. 726, Seattle, Wash. *Colonel, M.C.; Associate Professor of Physiology, Washington University Medical School, St. Louis, Mo.* (1, 1923)

White, Julius, A.M., Ph.D. National Cancer Institute, Bethesda, Md. *Senior Biochemist.* (*At present on leave of absence while in Army of U. S.*) (2, 1937)

White, Paul Dudley, M.D., Massachusetts General Hospital, Boston. *Lecturer in Medicine, Harvard Medical School; Physician (in charge of Cardiac Clinics and Laboratory), Mass. General Hospital.* (3, 1921)

Whitehead, Richard W., M.A., M.D. University of Colorado School of Medicine, 4200 E. Ninth Ave., Denver. *Professor of Physiology and Pharmacology.* (1, 1933; 3, 1928)

Wiener, Alexander S., M.D. 64 Rutland Rd., Brooklyn, N. Y. *Bacteriologist and Serologist to Office of Chief Medical Examiner of New York City; Head of Transfusion Division, Jewish Hospital of Brooklyn.* (6, 1932)

Wiersma, Cornelis A. G., M.A., Ph.D. California Institute of Technology, Pasadena. *Associate Professor of Physiology.* (1, 1941)

Wiggers, Carl J., M.D., Sc.D. Medical School, Western Reserve University, Cleveland, O. *Professor and Director of Physiology.* (1, 1907; 3, 1909)

Wiggers, Harold C., Ph.D. College of Medicine, University of Illinois, 1853 W. Polk St., Chicago. *Associate Professor of Physiology.* (1, 1938)

Wigodsky, Herman S., Ph.D., M.D.* Research Division, Air Surgeon's Office, Hdqtrs. of the Army Air Forces, War Department, Washington, D. C. *Major, M.C.; Chief, Physiological Branch.* (1, 1943)

Wikler, Abraham, M.D. U. S. Public Health Service Hospital, Lexington, Ky. *Surgeon (R), U. S. Public Health Service.* (3, 1944)

Wilde, Walter S., Ph.D.* Louisiana State University Medical School, New Orleans. *Assistant Professor of Physiology.* (1, 1944)

Wilder, Russell M., Ph.D., M.D. Mayo Clinic, Rochester, Minn. *Professor of Medicine, Mayo Foundation, University of Minnesota.* (1, 1921; 4, 1924; 5, 1933)

Wiley, Frank H., M.S., Ph.D. Food and Drug Administration, Federal Security Agency, Washington 25, D. C. *Senior Chemist.* (2, 1933)

Wilhelmi, Alfred E., Ph.D. 333 Cedar St., New Haven, Conn. Yale University School of Medicine. *Assistant Professor of Physiological Chemistry.* (2, 1942)

Wilhelmj, Charles Martel, M.D. Creighton University School of Medicine, Omaha, Neb. *Professor of Physiology.* (1, 1931)

Wilkerson, Vernon A., M.D., Ph.D. Howard University Medical School, Washington, D. C. *Professor and Head of Department of Biochemistry.* (2, 1936)

Williams, Edwin G., M.D., D.T.M., D.T.H. U. S. Public Health Service Hospital, Lexington, Ky. *Senior Surgeon U. S. Public Health Service, Director of Research, U.S.P.H.S. Hospital.* (3, 1944)

Williams, Harold H., Ph.D. 660 Frederick St., Detroit, Mich. *Associate Director, Research Laboratory, Children's Fund of Michigan.* (2, 1938; 5, 1936)

Williams, Horatio B., M.D., Sc.D. Box 893, Greenwich, Conn. *Dalton Professor of Physiology Emeritus, Columbia University.* (1, 1912)

Williams, J. W., M.S., Ph.D. University of Wisconsin, Chemistry Bldg., Madison. *Professor of Chemistry.* (2, 1944)

Williams, Ray D., M.D. 6834 Waterman St., St. Louis, Mo. *Research Fellow.* (5, 1941)

Williams, Robert R., D.Sc. Bell Telephone Laboratories, 297 Summit Ave., Summit, N. J. *Chemical Director.* (5, 1941)

Williams, Robert Hardin, M.D. Thorndike Laboratory, Boston City Hospital, Boston, Mass. *Associate in Medicine, Harvard Medical School; Assistant Physician, Thorndike Memorial Laboratory; Junior Visiting Physician, II and IV Medical Services (Harvard) Boston City Hospital.* (4, 1940)

Williams, Robert R., M.S., D.Sc. 297 Summit Ave., Summit, N. J. *Chemical Director, Bell Telephone Laboratories.* (2, 1919)

Williams, Roger J., Ph.D., D.Sc. University of Texas, Department of Chemistry, Austin. *Professor of Chemistry; Director, Biochemical Institute.* (2, 1931)

Wills, J. H., M.S., Ph.D.* University of Rochester, School of Medicine and Dentistry, Rochester, N. Y. *Associate in Pharmacology.* (1, 1943)

Wilson, David Wright, M.S., Ph.D. University of Pennsylvania Medical School, Philadelphia. *Benjamin Rush Professor of Physiological Chemistry.* (1, 1915; 2, 1915)

Wilson, Frank N., M.D. University Hospital, Ann Arbor, Mich. *Professor of Medicine, University of Michigan.* (4, 1925)

Wilson, Karl M., M.D. University of Rochester, School of Medicine, Rochester, N. Y. *Professor of Obstetrics and Gynecology.* (4, 1927)

Wilson, P. W., Ph.D. Department of Agricultural Bacteriology, University of Wisconsin, Madison. *Associate Professor in Agricultural Bacteriology.* (2, 1939)

Wilson, Robert H., Ph.D. U. S. Dept. of Agriculture, Western Regional Research Laboratory, 800 Buchanan St., Albany, Calif. *Pharmacologist.* (3, 1937)

Winder, Claude V., Sc.D. 1927 Dexter Ave., Ann Arbor, Mich. *Pharmacologist, Parke, Davis & Company, Detroit, Mich.* (1, 1938)

Windle, William Frederick, Ph.D. Northwestern University Medical School, 303 E. Chicago Ave., Chicago, Ill. *Professor of Anatomy.* (1, 1937)

Winkenwerder, Walter LaF., M.D. Brooklandville, Md. *Associate in Medicine, Johns Hopkins Medical School.* (6, 1938)

Winkler, Alexander Woodward, A.M., M.D. New Haven Hospital, 789 Howard Ave., New Haven, Conn. *Assistant Professor of Medicine, Yale University School of Medicine.* (1, 1940)

Winter, Charles A., Ph.D. University of Oklahoma, School of Medicine, 801 E. 13th St., Oklahoma City. *Assistant Professor of Physiology.* (1, 1940)

Winter, Irwin Clinton, Ph.D., M.D. University of Oklahoma School of Medicine, Oklahoma City. *Associate Professor in Pharmacology; Captain, M.C.* (3, 1941)

Winters, Jet C., M.A., Ph.D. University of Texas, Austin. *Professor of Home Economics.* (5, 1933)

Winternitz, M. C., M.D. Yale University School of Medicine, New Haven, Conn. *Anthony N. Brady Professor of Pathology.* (4, 1913)

Wintersteiner, Oskar, Ph.D. The Squibb Institute for Medical Research, New Brunswick, N. J. *Head, Division of Organic Chemistry; Honorary Professor of Biochemistry, Rutgers University.* (2, 1930)

Wintrobe, Maxwell Myer, M.D., Ph.D. University of Utah School of Medicine, Salt Lake City. *Professor and Head of the Department of Internal Medicine.* (4, 1940)

Wiseman, Bruce Kenneth, M.D. Kinsman Hall, Ohio State University, Columbus. *Professor of Medicine; Assistant Director of Medical Research.* (4, 1932)

Wislocki, George B., M.D. Harvard University Medical School, 25 Shattuck St., Boston, Mass. *Parkman Professor of Anatomy.* (1, 1924)

Witebsky, Ernest, M.D. Buffalo General Hospital, 100 High St., Buffalo, N. Y. *Professor of Bacteriology and Immunology.* (6, 1935)

Witzemann, Edgar J., M.A., Ph.D. Service Memorial Building, University of Wisconsin, Madison. *Associate Professor of Physiological Chemistry.* (2, 1925)

Wolbach, S. Burt, M.D. Harvard University Medical School, 25 Shattuck St., Boston, Mass. *Shattuck Professor of Pathological Anatomy; Member, National Academy of Sciences.* (4, prior to 1920)

Wolff, Harold G., M.D., M.A. New York Hospital, 525 E. 68th St., New York City. *Associate Professor of Medicine, Cornell University Medical College; Associate Attending Physician, New York Hospital.* (1, 1930; 3, 1942)

Wood, Earl H., M.S., Ph.D., M.D.* Mayo Aeromedical Unit, Mayo Foundation, Rochester, Minn. *Assistant in Physiology.* (1, 1943)

Wood, Harland G., Ph.D. Dept. of Physiology, University of Minnesota, Minneapolis. *Associate Professor, Physiological Chemistry.* (2, 1944)

Wood, Horatio C., Jr., M.D., Ph.M. 319 S. 41st St., Philadelphia, Pa. *Professor of Pharmacology and Therapeutics, University of Pennsylvania; Professor of Materia Medica, Philadelphia College of Pharmacy and Science.* (3, 1908)

Woodbury, Robert A., Ph.D., M.D. University of Georgia, School of Medicine, Augusta. *Professor of Pharmacology.* (1, 1936; 3, 1941)

Woodruff, Lorande Loss, A.M., Ph.D. Yale University, New Haven, Conn. *Professor of Protozoology; Member, National Academy of Sciences.* (1, 1910)

Woods, Alan C., M.D. Wilmer Institute, Johns Hopkins Hospital, Baltimore, Md. *Ophthalmologist-in-Chief; Acting Professor of Ophthalmology, Johns Hopkins University; Director, Wilmer Ophthalmological Institute.* (6, 1918)

Woods, Ella, A.M., Ph.D. University of Idaho, Moscow. *Home Economist, Experiment Station.* (2, 1925; 5, 1933)

Woodward, Alvalyn E., M.S., Ph.D. University of Michigan, Ann Arbor. *Assistant Professor of Zoology.* (1, 1932)

Woodyatt, Rollin T., M.D. 237 E. Deleware Place, Chicago, Ill. *Professor of Medicine, Rush Medical College, University of Chicago.* (2, 1912)

Woolley, Dillworth W., Ph.D. Rockefeller Institute for Medical Research, 66th St., and York Ave., New York City. *Fellow.* (5, 1941)

Woolsey, Clinton N., M.D. Johns Hopkins University School of Medicine, Baltimore, Md. *Associate in Physiology.* (1, 1938)

Wright, Angus, M.D. University of Southern California Medical School, 657 S. Westlake Ave., Los Angeles. *Pathologist, California Hospital.* (4, 1935)

Wright, Arthur W., M.D. Albany Medical College, New Scotland Ave., Albany, N. Y. *Professor of Pathology and Bacteriology.* (4, 1941)

Wright, Charles Ingham, M.S., Ph.D. National Institute of Health, Bethesda, Md. *Senior Pharmacologist, U. S. Public Health Service.* (1, 1935; 3, 1936)

Wright, George G., Ph.D. Dept. of Chemistry, California Institute of Technology, Pasadena. *National Research Fellow.* (6, 1943)

Wright, Harold N., M.S., Ph.D. University of Minnesota, Minneapolis. *Associate Professor of Pharmacology.* (3, 1933)

Wright, Sydney L., M.A., Ph.D. Endsmeet Farm Glenside, Pa. (2, 1933)

Wulzen, Rosalind, M.S., Ph.D. Oregon State College, Corvallis. *Assistant Professor of Zoology.* (1, 1916)

Wyckoff, Ralph W. G., Ph.D. School of Public Health, University of Michigan, Ann Arbor. (6, 1940)

Wyman, Jeffries, Jr., Ph.D. Harvard University, Cambridge, Mass. *Associate Professor of Zoology and Chairman of the Board of Tutors in Division of Biology.* (1, 1928)

Wyman, Leland C., Ph.D. Boston University School of Medicine, Boston, Mass. *Associate Professor of Physiology.* (1, 1927)

Wynne, Arthur M., M.A., Ph.D., F.R.S.C. Department of Biochemistry, University of Toronto, Toronto, Canada. *Professor of Biochemistry.* (2, 1940)

Yerkes, Robert M., Ph.D. Yale Laboratories of Primate Biology, 333 Cedar St., New Haven, Conn. *Professor of Psychobiology, Yale University; Member of the National Academy of Sciences.* (1, 1904)

Yonkman, Frederick F., Ph.D., M.D. Ciba Pharmaceutical Products, Inc., Summit, N. J. *Chief Pharmacologist.* (3, 1931)

Youmans, William Barton, M.A., Ph.D. University of Oregon Medical School, Portland. *Professor of Physiology.* (1, 1939)

Young, A. G., Ph.D., M.D. 520 Commonwealth Ave., Boston, Mass. *Assistant Professor of Therapeutics, Boston University School of Medicine; Medical Director, Corey Hill Hospital, Brookline.* (3, 1925)

Young, E. G., Ph.D., F.R.S.C. Dalhousie University, Halifax, N. S., Canada. *Professor of Biochemistry.* (2, 1925)

Youngburg, Guy E., M.S., Ph.D. 66 Park Circle, Eggertsville, Buffalo, N. Y. *Professor of Biological Chemistry, University of Buffalo.* (2, 1927)

Yuile, Charles L., M.D., C.M. Pathological Institute, McGill University, Montreal, Canada. *Assistant Professor of Pathology.* (4, 1941)

Zechmeister, L. California Institute of Technology, Pasadena. *Professor of Organic Chemistry.* (2, 1941)

Zeckwer, Isolde T., M.D. School of Medicine, University of Pennsylvania, Philadelphia. *Assistant Professor of Pathology.* (1, 1934; 4, 1927)

Zimmerman, Harry M., M.D., Lt. Comdr. (M.C.) USNR 1584 Boulevard, New Haven, Conn. (4, 1933)

Zwemer, Raymund L., Ph.D. 5003 Battery Lane, Bethesda 14, Md. College of Physicians and Surgeons, Columbia University, 630 W. 168th St., New York City. *Assistant Professor of Anatomy. On leave: Dept. of State, Washington, D. C.* (1, 1930)

Summary of Membership

The American Physiological Society	878
The American Society of Biological Chemists	638
The American Society for Pharmacology and Experimental Therapeutics	307
The American Society for Experimental Pathology	295
The American Institute of Nutrition	271
American Association of Immunologists	265
Total Members by Societies	2654

DECEASED MEMBERS

Abel, John J. (1, 2, 3) May 26, 1938.
Abbott, A. C. (1) September 11, 1936.
Abramson, H. L. (6) April, 1934.
Adami, J. George (2) August 29, 1926.
Adler, Herman M. (2) December 6, 1935.
Adler, Isaac (3) February 2, 1912.
Alsberg, Carl L. (1, 2) October 31, 1940.
Apfelbach, Carl Wesley (4) June 25, 1943.
Armsby, H. P. (1) October 19, 1921.
Atkinson, Harry V. (3) May 7, 1939.
Atwater, W. O. (1) September 22, 1907.
Austin, William C. (2) November 20, 1935.
Bancroft, F. W. (1) August 23, 1924.
Banting, F. G. (3) February 21, 1941.
Banzhaf, Edwin J. (2, 6) March 17, 1931.

Barbour, Henry Gray (1, 2, 3) September 23, 1943.
Benedict, Stanley R. (1, 2) December 21, 1936.
Bergmann, Max (2) November 7, 1944.
Beyer, Henry G. (1) December 9, 1918.
Black, Otis Fisher (2) October 14, 1933.
Blackfan, Kenneth D. (5) November 5, 1941.
Bleile, Albert M. (1) August 16, 1933.
Bodansky, Meyer (2) June 14, 1941.
Bowditch, Henry P. (1) March 13, 1911.
Braman, Winfred W. (5) March 24, 1937.
Brodie, Maurice (6) May 9, 1939.
Brodie, Thomas G. (1, 2) August 20, 1916.
Brown, Wade H. (3, 4) August 4, 1942.
Brubaker, Albert P. (1) April 29, 1943.
Bull, Carroll G. (6) May 30, 1931.
Bullowa, Jesse G. M. (3, 6) November 9, 1943
Burget, G. E. (1) June 4, 1938.
Busch, Fred C. (1) January 3, 1914.
Callison, William E. (3) February 26, 1937.
Carrel, Alexis (1, 4) November 5, 1944.
Cattell, J. McKeen (1) January 20, 1944.
Chapman, Henry C. (1) September 7, 1909.
Chillingworth, F. P. (1) June 30, 1938.
Chittenden, Russell H. (1, 2, 5) December 6, 1943.
Clark, Admont Halsey (1) October 13, 1918.
Clark, Earl P. (2) November 7, 1943.
Clark, G. P. (1) September 1, 1907.
Clarke, J. Alexander (6) 1943.
Cleghorn, Allen M. (1) March 20, 1916.
Cohen, Seymour J. (3) June 11, 1942.
Connor, Charles L. (4) June 12, 1941.
Cook, Frank C. (2) June 19, 1923.
Coombs, Helen C. (1, 3) March 4, 1944.
Coulter, Calvin B. (4) May 10, 1940.
Crawford, Albert C. (3) March 14, 1921.
Crile, George W. (1, 3) January 7, 1943.
Cullen, Glenn E. (2, 5) April 11, 1940.
Curtis, John G. (1) September 20, 1913.
Cushing, Harvey (1, 4) October 7, 1939.
Cushny, A. R. (1) February 25, 1926.
Dalton, J. C. (1) February 12, 1889.
Dastré, A. (1h) October 25, 1917.
D'Aunoy, Joseph Rigney (4) September 17, 1941.
Davis, Alice Rohde (2) August 22, 1933.
Dawson, Wilfred T. (1, 3) September 19, 1939.
Denis, Willey (1, 3) January 9, 1929.
Donaldson, Henry H. (1) January 24, 1938.
Dooley, David H. (1) April 11, 1927.
Dreyer, George P. (1) February 27, 1931.
Dunham, Edward K. (2) April 16, 1922.
Dusser de Barenne, J. G. (1, 3) June 9, 1940.
Edmunds, Charles W. (1, 3) March 1, 1941.
Englemann, Th. W. (1h) May 20, 1909.
Ets, Harold N. (1, 3) June 25, 1943.
Ewing, Ephraim MacDonald (1) August 27, 1925.
Fitch, Richard H. (1, 3) January 7, 1939.
Fitz, George W. (1) October 28, 1934.
Folin, Otto (1, 2, 3) October 26, 1934.
Foster, Nellis Barnes (2) August 20, 1933.
Franz, Shepherd Ivory (1) October 14, 1933.
Gager, C. Stuart (2) August 9, 1943.
Gates, Frederick L. (3, 4) June 17, 1933.
Gay, Frederick P. (4, 6) July 14, 1939.
Goodale, George L. (1) April 12, 1923.
Gortner, Ross A. (2) September 30, 1942.
Greeley, A. W. (1) May 15, 1904.
Gross, Louis (4) October 17, 1937.
Hall, G. Stanley (1) April 24, 1924.
Halsted, William S. (4) September 7, 1922.
Hammersten, O. (1h) September 21, 1932.
Harding, Victor John (2) July 10, 1934.
Hare, Hobart Amory (1) June 15, 1931.
Haskins, Howard Davis (1, 2) November 19, 1933.
Hatcher, Robert A. (1, 2, 3) April 1, 1944.
Hawkins, James A., (1, 2) July 26, 1937.
Henderson, Lawrence J. (1, 2) February 10, 1942.
Henderson, Yandell (1, 2, 3) February 19, 1944.
Herter, C. H. (1) December 5, 1910.
Hess, Alfred Fabian (2, 5) December 5, 1933.
Hewlett, Albion Walter (1, 3, 4) November 10, 1925.
Hirschfelder, Arthur D. (1, 2, 3) October 11, 1942.
Hiss, Philip H., Jr. (2, 3) February 27, 1913.
Hofmeister, F. (1h) July 26, 1922.
Hooper, Charles Warren (1) January 27, 1936.
Hough, Theodore (1) November 30, 1924.
Howland, John (2) June 20, 1926.
Huber, G. Carl (1) December 26, 1934.
Hyde, Roscoe R. (6) September 15, 1943.
Inman, Ondess L. (2) July 21, 1942.
Jackson, Holmes C. (1, 2) October 25, 1927.
Jaffe, Hermann R. (4, 6) December 17, 1937.
James, Wm. (1) August 26, 1910.
Jenkins, Oliver P. (1) January 9, 1935.
Jones, Frederic S. (4) October 19, 1934.
Jones, Walter (1, 2) February 28, 1935.
Jordan, Edwin O. (1) September 2, 1936.
Joseph, Don R. (1, 3) July 9, 1928.
Julianelle, Louis A. (6) August 12, 1944.
Kahn, Max (2) April 8, 1926.
Kastle, Joseph H. (1, 2) September 24, 1916.
King, Walter E. (6) May 1, 1936.
Klotz, Oskar (4) November 3, 1936.
Koch, Waldemar (3) February 2, 1912.
Koessler, Karl K. (2, 4, 6) February 13, 1928.
Koller, C. (3h) March 21, 1944.
Krause, Allen K. (4) May 12, 1941.
Kriss, Max (5) November 15, 1941.
Krumwiede, Charles (6) December 29, 1930.
Landsteiner, Karl (4, 6) June 26, 1943.
Langley, J. N. (1) November 5, 1925.
Langworthy, Charles F. (2) March 3, 1932.
Lee, Frederic S. (1) December 14, 1939.
Leech, Paul Nicholas (3) January 14, 1941.
Levene, Phoebus A. (1, 2) September 6, 1940.
Lewis, Dean (1) October 9, 1941.
Lewis, Paul A. (3, 4, 6) June 30, 1929.
Lingle, D. J. (1) November 27, 1936.
Loeb, Jacques (1, 2) February 11, 1924.

Loevenhart, A. S. (1, 2, 3) April 20, 1929.
Long, John H. (2) June 14, 1918.
Lombard, Warren P. (1) July 13, 1939.
Lusk, Graham (1, 2, 5) July 18, 1932.
Lyon, Elias P. (1) May 4, 1937.
Macallum, Archibald Byron (1, 2) April 5, 1934.
Macleod, John James Rickard (1) March 16, 1935.
McCordock, Howard A. (4) November 13, 1938.
McDonald, Claude H. (1) 1944:
McGlone, Bartgis (1) November 10, 1941.
McKinley, Earl B. (4, 6) July 28, 1938.
Magnus, Rudolf (3) July 25, 1927.
Mall, Franklin P. (1) November 17, 1917.
Mallory, F. B. (4) September 28, 1941.
Mandel, John A. (1, 2) May 5, 1929.
Mann, Gustav (1) July 18, 1921.
Marriott, W. McKim (2, 5) November 11, 1936.
Marshall, John (1, 2) January 5, 1925.
Martin, Ernest Gale (1) October 17, 1934.
Martin, H. Newell (1) October 27, 1896.
Matson, Ray W. (6) September, 1934.
Mathews, Samuel A. (1, 3) February 19, 1928.
Maximow, Alexander A. (4) December 4, 1928.
Maxwell, S. S. (1) January 28, 1939.
Meigs, Edward B. (1, 2, 5) November 5, 1940.
Mellus, E. Linden (1) December 17, 1923.
Meltzer, S. J. (1, 2, 3, 4) November 7, 1920.
Mendel, Lafayette B. (1, 2, 3, 5) December 9, 1935.
Meyer, Hans H. (3h) October 6, 1939.
Miller, Elmer S. (2) June 11, 1941.
Miller, Joseph L. (1, 3) August 6, 1937.
Mills, Thomas W. (1) February 13, 1915.
Minot, Charles S. (1) November 19, 1914.
Mitchell, S. Weir (1) January 4, 1914.
Moore, Lillian Mary (1) August 1, 1929.
Morris, J. Lucien (2) March 19, 1926.
Moyer, Laurence S. (2) June 8, 1942.
Myers, Harold B. (3) March 16, 1937.
Neuhausen, Benj. S. (2) August 20, 1923.
Nelson, Louis (3) April 14, 1912.
Nichols, Henry J. (4) September 2, 1927.
Noguchi, Hideyo (4, 6) May 21, 1928.
Osborne, Thomas Burr (1, 2) January 29, 1929.
Osler, Sir William (1) December 29, 1919.
Ott, Isaac (1, 3) January 1, 1916.
Palmer, LeRoy S. (2, 5) March 8, 1944.
Park, William H. (4, 6h) April 6, 1939.
Pavlov, Ivan P. (1h) February 27, 1936.
Pearce, Richard M., Jr. (4) February 16, 1930.
Perla, David (4, 6) June 14, 1940.
Peters, H. C. (1) July 13, 1942.
Pettibone, C. J. V. (2) March 8, 1929.
Pfaff, Franz (1, 2) September 26, 1926.
Pflüger, E. (1h) March 17, 1910.
Pincussen, Ludwig (2) November 30, 1941.
Plant, Oscar H. (1, 3) October 1, 1939.
Prince, Alexander L. (1) May 25, 1938.
Ranson, S. W. (1) August 30, 1942.
Reichert, Edward T. (1) December 25, 1931.
Richards, Herbert M. (2) January 9, 1928.
Robertson, T. Brailsford (2) January 27, 1930.
Rockwood, Elbert W. (2) July 17, 1935.
Rosenbloom, Jacob (2) September 25, 1923.
Rose, Mary Schwartz (1, 2, 5) February 1, 1941.
Ross, Ellison, L. (2, 3) December 21, 1938.
Rowe, Allan Winter (1, 2, 5) December 6, 1934.
Rutan, Robert F. (2) February 19, 1930.
Salant, William (1, 2, 3) December 10, 1943.
Schafer, Sir Edward Sharpey (1h) March 29, 1935.
Schiff, Fritz (6) 1940.
Schlutz, F. W. (2, 5) March 8, 1944.
Schoenheimer, Rudolf (2) September 11, 1941.
Scott, J. M. Duncan (1) January 28, 1930.
Sedgwick, William T. (1) January 26, 1921.
Sellards, Andrew Watson (4) December 1, 1942.
Sewall, Henry (1) July 8, 1936.
Shaw, Louis A. (1) August 27, 1940.
Sheldon, Ralph E. (1) July 9, 1918.
Shorey, Edmund C. (2) January 30, 1939.
Simon, Charles E. (1, 2) November 8, 1927.
Sinclair, A. N. (6) October 21, 1930.
Simpson, G. E. (2) December 23, 1927.
Simpson, Sutherland (1) March 2, 1926.
Smith, H. E. (1) October 9, 1933.
Smith, R. Meade (1) 1919.
Smith, Theobald (4h, 6) December 10, 1934.
Spaeth, Reynold A. (1) January 26, 1925.
Spencer, Henry James (5) 1944.
Sternberg, G. M. (1) November 3, 1915.
Stevens, Herman C. (1) May 27, 1934.
Stewart, Colin C. (1) January 22, 1944.
Stewart, G. N. (1, 3, 4) May 28, 1931.
Stiles, Percy G. (1) July 5, 1936.
Storey, Thomas A. (1) October 27, 1943.
Straus, Henry W. (6) 1937.
Terry, Oliver P. (1) December 6, 1933.
Thatcher, Roscoe Wilfred (2) December 6, 1933.
Thompson, Wm. G. (1) October 27, 1927.
Trask, James D. (6) May 24, 1942.
Underhill, Frank P. (1, 2, 3) June 28, 1932.
Van Slyke, Lucius L. (2) September 30, 1931.
Vaughan, Victor C. (1, 4) October 21, 1929.
Vincent, S. (1) December 31, 1933.
Von Brücke, Ernest T. (1) June 12, 1941.
von Voit, C. (1h) January 31, 1908.
Wallace, Edward W. (3) July 11, 1943.
Walton, D. C. (3) March 6, 1942.
Warren, Joseph W. (1) December 20, 1916.
Warthin, Aldred Scott (4) May 23, 1931.
Webster, Leslie T. (4) July 12, 1943.
Webster, Ralph W. (2) July 2, 1930.
Weil, Richard (3, 6) November 19, 1917.
Weiss, Soma (3) January 31, 1942.
Welch, William H. (1, 4h) April 30, 1934.
Wells, H. Gideon (2, 4, 6) April 26, 1943.
Westbrook, Frank F. (1) October 21, 1918.
Wherry, William Buchanan (4) November 1, 1936.
Wiley, Harvey W. (2) June 30, 1930.
Woelfel, A. (1) January 31, 1920.
Wood, Horatio C. (1) January 3, 1920.
Zinsser, Hans (4, 6) September 4, 1940.

INDEX

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